# A STUDY OF THE DICK TEST IN SCARLET FEVER. A CONSIDERATION OF THE ANOMALIES OF THE TEST AND OF THE SIGNIFICANCE OF SKIN SENSITIVITY TO PRODUCTS OF THE HAEMOLYTIC STREPTOCOCCUS.

by

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# C O N T E N T S.

## (PART II)

The skin reaction in scarlet fever and in other conditions to an intracellular extract of the haemolytic streptococcus freed from all diffusible substances.

## PART I.

The skin reaction in scarlet fever to a diffusible extracellular product of the haemolytic streptococcus (Dick toxin).

# INTRODUCTION.

It is now nearly half a century since Klein [35], in 1885, succeeded in isolating streptococci from the blood of scarlet fever patients. His contention that the streptococcus was the causal organism was not generally accepted at the time; indeed, until 1923 his theory received little support. The work of Gabritchewsky [37] with streptococcal vaccines revived some interest in 1905, and the Schultz-Charlton reaction was described in 1918, but it was the interpretation by Mair of the latter phenomenon in 1923 as a toxin-antitoxin reaction, followed by the publication of the work of George and Gladys Dick a little later, which firmly established the haemolytic streptococcus in the rôle of the primary invader.

The classic work of the Dicks appeared to crown with success forty years of human endeavour, and to close one of the most interesting chapters in the history of medicine. At the same time it presented both to the clinician and to the epidemiol: :ogist vistas rich in promise of specific treatment and specific prophylaxis.

This year the Cameron Prize has been awarded to the Dicks for their brilliant studies. In the /

the ten years which have elapsed since they were published, these studies have been subjected to a growing volume of criticism. Workers of repute in many parts of the world believe that our present conception of scarlet fever, based, as has been indicated, almost entirely on the work of the Dicks, is fundamentally inaccurate, and that the test of susceptibility which bears their name, is fallacious in theory and valueless in practice. The paradoxical behaviour of the Dick test has always given rise to a degree of criticism. During recent years the wealth of anomalous findings reported in the literature has so accumulated, and attempts to explain these anomalies have proved to some workers so unsatisfactory, that by them the Dicks' work has been discredited, and their test as a practical measure discarded.

If this test of susceptibility is indeed invalid, as the most casual perusal of the continental literature would imply, then we must revise our present conception of the disease and start again, ab initio, to build up the fabric of truth. If, on the other hand, the conception which is based on their work is fundamentally sound, any attempt to assess the frequency and significance of these anomalies /

anomalies in actual practice becomes a procedure of some value.

That they constitute a subject of academic interest is unquestionable. To the writer it appears that their consideration raises problems of considerable practical importance.

## OUTLINE OF PRESENT STUDY.

The first part of the work deals with the employment of a filtrate derived from a haemolytic streptococcus as originally described by the Dicks. An account of their work will be followed by a brief review of the results which other workers employing their methods have obtained. No attempt will be made to include all the results which have appeared in the literature since 1923, but it will be necessary to consider a proportion of this work, if only to illustrate the remarkable lack of uniformity in the results obtained. It is this lack of agreement between workers of repute which has formed the stimulus for the present study.

The latter has taken the form of a clinical investigation of the Dick reaction in 160 cases of scarlet fever, not in different patients at different stages of the illness, but following the changes in the reaction throughout the course of the disease. Each case was tested on admission and every test repeated in each week, either until the patient was discharged from hospital, or until six weeks had elapsed. The methods employed will be described, the results I have obtained presented, and these briefly /

briefly summarised.

The summary of the present investigation is followed by a discussion of these results and of the various difficulties in connection with the test which they illustrate. I have endeavoured to account for the discrepancies in the results of different workers, to assess the relative importance of the difficulties which these results raise, and finally to draw conclusions as to the validity of the test and its application to the whole problem of scarlet fever.

The second part of the study concerns the employment of a further product of the haemolytic streptococcus, but one prepared by an entirely different method and possessing vastly different properties. The material was prepared by Dr. H.J. Gibson of the University Bacteriology Department and the cutaneous reactions which it produced in cases of scarlet fever appeared to Dr. Gibson and myself to be of such an interesting nature, as to merit publication in view of certain other papers which have appeared recently in connection with rheumatic infection. We therefore reported in the form of a short /

short paper the results obtained in some 20 odd cases.

Since then I have had an opportunity of extending this work. I have been able to investigate the reaction to this type of preparation in approximately half of the scarlet fever cases which have formed the basis of the first part of this thesis, and also in 160 persons not suffering from scarlet fever. Some of these persons were apparently healthy, while othere were suffering from a wide variety of complaints. I propose in this thesis to give some account of these extended results. First I wish to indicate the purport of the work, both as a natural sequal to recent writings, and more particularly in an effort to establish its relationship, if any, to the anomalies of the Dick test which have already been considered. In a discussion of these results I wish to refer partic: :ularly to scarlatinal nephritis and scarlatinal arthritis, and to the possible association between scarlet fever and acute rheumatism. The results I have obtained in a preliminary series of cases of erysipelas and puerperal infection are of considerable interest and indicate the need for fuller investigation.

## THE WORK OF THE DICKS AND DESCRIPTION OF THE DICK TEST. THE SCHULTZ-CHARLTON PHENOMENON AS A TOXIN-ANTITOXIN REACTION.

In 1923 Dr. George F. Dick and Dr. Gladys H. Dick (30) of Chicago reported the result of a series of inoculation experiments which have since become classical. They obtained some pus from the sore finger of a nurse, who had contracted scarlet fever, and from it isolated a pure culture of a haemolytic streptococcus with which they then inoculated the throats of ten volunteers. These were all young adults, who said that they had not had the disease. Two of them developed the disease in typical form. In one of these cases previous inoculation with a Berkefeld-V filtrate of the organism had failed to produce the disease.

The failure of the other persons to acquire scarlet fever suggested some difference in susceptibility, and the Dicks proceeded to follow up their work by using a filtrate of the same streptococcus for intracutaneous injection. A Berkefeld-W filtrate was diluted 1:1000 in sterile salt solution, and of this 0·1cc. was injected into the /

the skin on the anterior surface of the forearm by means of a small record syringe and a No. 26 needle. The small wheal that resulted disappeared in a few minutes. In a series of 153 cases some showed no reaction whatever. Others gave varying degrees of reddening and swelling about the site of the inoculation. The positive reactions usually began to appear from four to six hours after the inoculation. At first they consisted of a small circular area of erythema. This red area increased, and reached a maximum size and intensity between eighteen and thirty-six hours after the injections. In the less strongly positive tests, the maximum was reached between eighteen and twenty-four hours. The reddening was frequently associated with some swelling of the skin. In the most strongly positive tests, the reddened area continued to spread, and the swelling increased up to about thirty-six hours after the inoculation. Soon after reaching their maximum size and intensity, the reactions began to subside. Even the most strongly positive did not persist after forty-eight hours. The bright red colour became dull and began to fade. The swelling disappeared. There was left only a faintly yellowish /

yellowish area. This area sometimes desquamated during the week or ten days following the test.

The reactions were observed at the end of twenty-four hours and classified as negative, slightly positive, positive and strongly positive, according to the size and intensity of the reaction, varying from a small area of trauma up to an intensely red swelling of over 3 cm. in one or both diameters.

As a control test they employed undiluted fluid from sterile culture medium. The following were their results in tabular form: (31)

| Subject | No. Tested. | Nega: :tive. | Slight Pos. | Pos. | Strong Pos. |
|---|---|---|---|---|---|
| Scarlatina Convalescents (7th to 33rd day of disease) | 65 | 62 | 3 | 0 | 0 |
| Persons with history of Scar: latina (6 months to 37 years before) | 16 | 15 | 0 | 0 | 1 (doubtful history) |
| Persons with no history of scarlatina. | 72 | 35 | 7 | 17 | 13 |

41.6% of the persons with no history of scarlatina /

scarlatina were thus found to be positive or strongly positive reactors. These types of reaction were never found in the convalescent patients.

In two instances in which it was possible to observe the test before and after an attack of scarlet fever, it was positive before the attack, and negative during convalescence.

They also made the extremely important observation that the action of the filtrate on the skin was inhibited by convalescent scarlet fever serum, mixed with the filtrate before it was injected, or given intramuscularly before the test was made. Their conclusion was that "the skin test described bears a specific relation to immunity to scarlet fever."

In a later paper (32) they showed that when persons with positive skin tests were injected with suitable quantities of the toxic filtrate they were liable to develop a scarlatinal rash with nausea, vomiting, rise in temperature, and general malaise, within a few hours after the injections. The active principle contained in the filtrate was relatively heat resistant, being only destroyed at a temperature between 85° and 100°C.

Following /

Following this injection and subsequent illness the skin test was greatly modified, indicating the production of some degree of active immunity to scarlet fever. The blood serum of such a person was then found to be capable of neutralising the toxic substance in the filtrate, and their conclusion was that the latter was a true toxin capable of forming an antitoxin.

In the following year (1925) a fourth paper (33) appeared, summarising much of their previous work and dealing mainly with their results in active immunization. They here described their methods of standardization of the toxin and of the skin test dose, and pointed out in this connection, that a highly immune person may show a negative reaction with 150 times the skin test dose of toxin, while the extremely susceptible person may react to a fraction of the skin test dose. As it was found that some skins reacted to the intradermal injection of even sterile salt solution with the formation of a small papule, they finally arranged the skin test dose so that any area of reddening less than 1 cm. in all diameters might be regarded as a negative reaction. In this paper they also stressed the variation in intensity met with in positive reactions. /

reactions. Early fading they regarded as an indication of partial immunity, and "if it is entirely faded at the end of 24 hours it is negative." The positive reaction varies from a faint pink flush to an intense bright red, which may be surrounded by a zone of pallor. Some reactions were of a rash type composed of red spots on a white background. Sometimes the lymphatics in the immediate vicinity of the skin test were outlined by pink streaks, and occasionally there was a rash in the bend of the elbow above the test.

Early in 1924 Branch and Edwards (8) were able to confirm the results obtained with Dick toxin in a further series of 148 persons, the only material difference being that Dick filtrate heated to 90°C. for 1 hour was used as a control in every case.

In the same year Zingher (83) published the results which he had obtained on a much larger scale. His paper and the more important of the papers which were to follow will be considered presently. Before leaving the Dicks' work and their new conception of scarlatina as a disease caused by a toxin with the subsequent elaboration in the body of an antitoxin and the acquisition of an immunity, it is interesting to /

to note, that Mair[65], in this country, arrived at this same conception by an opposite method of approach. His paper appeared in 1923, and was a new interpretation of the work of Schultz and Charlton as a toxin-antitoxin phenomenon.

Schultz and Charlton[74] in 1918 described the following skin reaction:

"If one injects intracutaneously into the skin of a scarlet fever patient with a bright rash 1 cc. of serum from a normal person or from a convalescent case of scarlet fever, there appears, after a time, at the site of the injection a characteristic change. This begins after about six hours and consists in a complete blanching of the rash over an area of from half an inch to a few inches in diameter. The area of pallor is usually circular or oval in shape, the margin being as a rule only slightly irregular. In the affected area the swollen follicles which are a feature of many rashes disappear. Looked at from a little distance the margin of the defect in the rash is generally pretty sharply defined. In one case we saw the contrast between the pale area and the surrounding rash heightened by a markedly hyperaemic margin. The colour /

colour of the blanched area is that of the normal skin. The duration of the phenomenon coincides, on the whole, with that of the rash itself; at any rate it may remain quite visible for several days." They found that this reaction could be obtained in the great majority of scarlet fever cases with a sufficiently well developed rash. In 46 cases they reported 40 positive reactions, five being doubtful, and one negative. They could detect no qualitative difference between the action of convalescent serum and that from "normal persons." On the other hand, the serum from scarlet fever patients during the acute stage of the illness invariably gave negative results. Between the fourteenth and nineteenth days of the disease they found that it had acquired, or, as they thought at the time, recovered its lost power of blanching the rash.

It was not till 1923 that Mair threw an entirely new light on the phenomenon which Schultz and Charlton had described. This was his interpretation:

"There is reason to believe that in scarlet fever there is concerned a toxin which presents certain points of resemblance to that of diphtheria." /

diphtheria." This toxin, he believed, interfered with the function of the cells of the contractile elements of the capillaries and caused a loss of tone, which resulted in the erythema and exudative phenomena of the scarlatinal rash. A positive reaction (blanching) following injection of serum was due to the contained antitoxin dislodging and neutralising the toxin fixed in the cells with restoration of normal function in 12-24 hours.

When the rash faded in a normal manner the mechanism was probably different, as this occurred long before any antitoxin could be demonstrated in the patient's blood. "It is known that over 80% of so called normal adults have appreciable amounts of diphtheria antitoxin in their blood, but we do not therefore assume, that the diphtheria patient has antitoxin in his blood before he is attacked, and that he suddenly loses this antitoxin on the first day of the disease. It is of course known that the diphtheria patient has no antitoxin or only inapprec: :iable traces in his blood, before he is attacked by the disease, and the same is no doubt true of scarlet fever. The reason for the negative Schultz-Charlton reaction, given by the serum of scarlet fever patients in the first fortnight of their illness /

illness, is simply that the necessary antitoxin has not yet had time to develop. It follows that when the serum of a so called normal person is found to give the reaction, this means, just as in the case of diphtheria, that the individual in question has acquired at least a certain degree of immunity to scarlet fever, either by an attack of the disease or by an atypical illness which could not be diagnosed as such, or possibly by a series of sub-infective immunising doses, or by a combination of these events."

In conclusion Mair stated that the nature of the Schultz-Charlton phenomenon could not be completely solved until something more was known of the cause of scarlet fever. In the meantime he considered the evidence in favour of the toxin-antitoxin hypothesis was sufficient to justify a more extensive investigation from this point of view. Such an investigation would throw light on the epidemiology of scarlet fever, just as the Schick test had done in the case of diphtheria. It seemed highly probable that the true causal micro-organism would be capable of producing a toxin, and, by the immunisation of animals, an antitoxin, and the latter /

latter should give the Schultz-Charlton reaction in man.

Mair's very shrewd observations have been quoted in some detail because of their obvious application to the work of the Dicks published in the same year. The latter appeared to at once remove Mair's conception from the realms of speculation to those of actual fact, so that this toxin-antitoxin theory became firmly established, and it has remained so during the last ten years in spite of much destructive criticism.

## THE RESULTS OBTAINED BY OTHER WORKERS.

Zingher (83) was the first worker to make a really intensive investigation of the test which the Dicks had described, and to report the results which he had obtained in actual practice. He studied the test in large numbers of apparently healthy persons and healthy families, and found that the reaction was a definite indication of susceptibility or immunity to scarlet fever, whether natural or following active immunization; further, that in normal persons the percentage of susceptibles by age groups and by social status resembled closely the percentage of persons susceptible to diphtheria noted with the Schick test. He introduced scarlet fever toxin intradermally into patients in the acute stage of the fever, and also into patients admitted to the Willard Parker Hospital, who were not suffering from scarlet fever. He found that the test was of considerable value in doubtful cases; a strong positive reaction early in the disease and still strongly positive when tested later, spoke against the diagnosis of scarlet fever; a definite negative during the first two days of the rash was an indication /

indication that one was not dealing with scarlet fever, as a negative reaction did not develop till the 6th or 10th day. His actual results were as follows:

(1) Of 141 scarlet fever patients in the first 5 days all gave a positive reaction, though the degree of redness varied and a markedly strong reaction was very scarce.

(2) After 6 days the positives had fallen to 16.

(3) Of 170 patients tested on admission and later in convalescence 93% of the positives became negative. Of the 12 patients who remained positive, only 2 gave positive Schultz-Charlton tests, and these he regarded as true cases of scarlet fever. In the other 10 there was an absence of desquamation and apparently an element of doubt.

These results and conclusions have been given in some detail because of their importance. It is because subsequent workers have been unable to fully substantiate them, that the subject has become controversial, and the actual mechanism of the Dick reaction remains still a matter of controversy.

In 1925 Joe (46) published some results which supported Zingher's work up to a point. His results /

results are given in the following table:

| Days | No. of Cases | Percentage Positive |
|---|---|---|
| 1-5 | 103 | 95 |
| 6-10 | 110 | 79 |
| 11-15 | 103 | 55 |
| 16-20 | 101 | 32 |
| 21-25 | 116 | 16 |
| 26-30 | 82 | 11 |
| 31-35 | 66 | 4·76 |
| 36-139 | 65 | 6·15 |

It will be seen that his percentage of positive reactions in the acute stage of the illness is high. In obtaining this high percentage he emphasized the importance of selecting a potent toxin before embarking on large scale testing, and he advanced the view, that the only satisfactory method of choice was by actual trial of different toxins in the disease itself. His suggestion was, that a reliable toxin should give 95% positive results before the fifth day, and at least 70% negative reactions by the thirtieth day. This question of strength of toxin in the interpretation of results obtained in the disease will be referred to again, but in passing, one may mention very briefly its enormous importance /

importance in scarlet fever prophylaxis. It is interesting to note that in the first paper published by Dr. Benson (3) on his prophylactic work at the Edinburgh City Hospital he was employing a "100%" toxin, - one that had actually given 50 positive reactions in 50 cases of scarlet fever in the acute stage. To return again to the consideration of Joe's results in comparison with those of Zingher, it will be seen that an enormous discrepancy exists in the second week of the disease. While only 16 of the American worker's 141 cases were still positive, the British figure of positives remained as high as 79%.

It is a striking fact that this figure obtained by Joe between the 6th and 10th day of illness is actually higher than the percentage of positives which the late Dr. Ker and his co-workers (50) obtained in the first 3 days of the disease. Ker, whose figures were obtained over a smaller number of cases and were published some months before those of Joe, found that 73% of positive reactions occurred during the first three days of illness.

In the same year Silcock (75) obtained 68% of positive reactions, also only over a small number of cases.

In /

In 1926 Harries (43) recorded 79% of early positive reactions. In 1927 Sutherland (77) claimed to have obtained a slightly higher figure, viz. 83% of positives, and showed how this figure could be raised very appreciably, if one were to include as positives a certain group of cases which were in doubt owing to the brilliance of the rash. This point will be referred to again in the consideration of the writer's own results.

Lichtenstein (56) published results obtained at Stockholm on a much larger series of 450 cases. Of these only 75% gave positive results "even to highly efficient toxins."

Jacobowitz (45), on the other hand, obtained only 57% of positives during the first five days, and he not unnaturally came to the conclusion, that the test was of little value in differential diagnosis.

The results reported by Peters and Allison (72) in 1928 were even more disturbing. Of their 131 patients, tested in the first 3 days of the disease, only 49% showed positive reactions, or to put the matter more forcibly, the majority of a series of acute scarlatina gave Dick negative reactions. /

reactions. Furthermore, of 194 convalescents no less than 31% were still Dick positive. They also described the case of a Dick negative nurse who took the disease, and was retested on the first day of illness, and found to be still negative.

There are many such cases reported in the literature and one may in this connection refer to a paper published by Lees (55). This worker described an outbreak of scarlet fever in an agricultural college of which 50% of the pupils were known to be Dick negative. 48 cases occurred, and of these, 68% were positive. In the negative patients nothing atypical in the clinical features or in the subsequent course of the disease could be found. 11 of these patients had been negative from the beginning, but 4 had been made negative by a brief course of immunisation. Those cases which were negative in the acute stage were all retested with different toxins with the same result. He concluded that either these Dick tests were not sufficiently testing, or else that they were dealing with multiple strains of toxin, one or more of which, was not included in the skin test. A small number of Schultz-Charlton tests were made, and all were positive, but he found that /

that the reaction took some time to develop and was best seen at 48 hours. He also found that the serum of convalescent cases gave earlier and more complete blanching than scarlet fever antitoxin, though both were used in the same quantity, 0.5 to 0.75 cc. Now most workers have found that specific antitoxin gives better results than convalescent serum even when used in small doses of 0.2 cc. The most obvious explanation is that the antitoxin used by Lees was inefficient. The fact that some 30% of the patients gave negative reactions in the acute stage of the illness is only in accordance with the experience of other workers already quoted. It is in no sense an extraordinary finding, although it may be somewhat difficult to explain. Far more striking, and far more difficult of explanation, is the fact that no fewer than 11 Dick negative persons developed scarlet fever. May this epidemic have been caused by a streptococcus which produced a toxin different from the toxin and antitoxin used in the skin tests? This hypothesis would explain both the anomalous results produced by the Dick test and the greater specificity of the convalescent serum, but it infers the existence of multiplicity of toxins. This possibility will /

will have to be considered again in light of more recent work.

So far, I have made no attempt to describe and consider all the anomalies which have been encountered in the behaviour of the Dick reaction, but have merely selected some of the more important papers which deal with the test in scarlet fever. I have shown that marked discrepancies exist. It is difficult to obtain from the continental literature results which are strictly comparable with these already quoted, but one can indicate the trend of opinion on the Continent by presenting quite briefly the views of von Gröer.

Von Gröer, Redlich and others (42), working at Lemberg, have apparently found the reaction to be so capricious, and results in individual cases so difficult to interpret, that they have come to the following conclusions. They maintain that Dick toxin is not a primary toxin in the true sense of the word, but merely a bacterial product with only slight toxic properties, which, however, may produce a violent reaction in a sensitive individual. Further: :more, this reaction not infrequently spontaneously changes in character within a short space of time, positives /

positives becoming negatives, and vice versa. In their opinion the Dick test is an essentially allergic reaction, and the results cannot be regarded as an indication of the presence or absence of antitoxic immunity to the scarlatinal toxin. The merits and demerits of this view, which appears to be widespread among Continental workers and has also considerable support in America, will be discussed later.

A very interesting series of papers has been recently published by a group of Japanese investigators working at the Government Isolation Hospital in Dairen (81). Some of their results are of great interest, and, if substantiated, form a definite advance as regards the significance and interpretation of the Dick test. Their work will be discussed more fully in the second part of this study. As regards the relative merits of the anaphylaxis theory, of which von Gröer is the chief supporter, and the more generally accepted toxin - antitoxin theory, they admit freely the difficulties of coming to any definite conclusion, although they have given the matter five years extensive study. Their figures, however, seem conclusive enough, in so far as over the largest series of cases yet published, they tally with those of Lichtenstein based on the second /

second largest series. Of the Japanese 1380 cases 75.8% were positive in the early stage of the illness. This conforms very closely with the Swedish figure of 75% already quoted.

Before considering the significance of the other figures already referred to, I propose to detail in the following pages my own experience with the Dick test.

## SCOPE OF PRESENT INVESTIGATION - MATERIAL AND METHODS EMPLOYED.

In the following pages will be found the results obtained in performing the Dick test on a series of 160 cases of scarlatina. Every case was tested on admission, and the test repeated at weekly intervals till discharge from hospital, or till six weekly readings were obtained. A control test was performed on admission in all cases, but if no trace of a pseudo-reaction was obtained, this was not repeated in the subsequent weeks. All the readings recorded were made at the end of 24 hours.

The material used was the ordinary commercial product of "Dick Toxin" and "Dick Control" supplied by Messrs. Borroughs, Wellcome & Co. The diluent used in this preparation is an isotonic buffered solution of borax, boric acid and saline in the proportions suggested by Glenny, Pope and Waddington (39). This acts as a preservative and is of value in the maintenance of a constant pH. It has been shown to give more satisfactory results than normal saline (O'Brien, Okell and Parish) (68). Dr. O'Brien tells me that the "Control" fluid is heated to 96°C. for two hours.

An /

An ordinary 1 cc. "Record" syringe was used for injection fitted with a small fine bore needle suitable for intradermal work. A firmly fitting needle, and a plunger which fits the barrel of the syringe accurately, are essential. Otherwise leakage is troublesome. Frequent boilings of the syringe are therefore to be avoided. It is important that no trace of antiseptic reach the material for injection. A simple, and in the writer's experience, satisfactory procedure, is to keep the syringe with needle attached quite dry. Before use the syringe is washed out repeatedly with methylated ether, and then thoroughly dried in air. When one is certain that all trace of ether has gone the syringe may be filled with the amount of toxin to be used. After cleansing the skin of the anterior aspect of the forearm with a little methylated ether 0.2 cc. of Toxin or Control is introduced intracutaneously in the usual manner. All tests proper were made in the left arm and control tests in the right. Two separate syringes were kept and these after use were again thoroughly cleansed with ether, and returned, with the needle still attached, to a box suitably padded with wool and fitted with a tight metal /

metal cover.

For the purpose of this study it is not necessary to include here clinical records of the cases. It was hoped that one might find some clinical features to account for variations in the skin reaction, particularly in the acute phase of the illness. Clinical notes were therefore taken of each case from this point of view, but as it has not been possible to correlate any variation in the skin reactions with any variation in the clinical picture they have not been included. In their place will be found an abstract giving the mean diameter in each week of the disease, along with the age of the patient, the day of disease on admission, and, where indicated, a brief remark regarding the clinical condition.

Every case recorded in this series was one of clinical scarlatina, in which it was possible to perform at least four Dick tests, one in each week of the disease. Any case admitted after the seventh day is therefore not included. Two cases with pseudo-reactions have also been excluded owing to the difficulty of their interpretation. There is one important respect, however, in which the clinical material must be regarded as selected. All were moderate /

moderate or mild attacks, as the routine administra:
:tion of antitoxic serum to all sharp cases rendered the inclusion of these impossible for the present purpose. Brown (11) in 1929 compared the results of Dick testing serum treated cases with untreated cases, and found, as one might expect, an immediate fall in positives from 69% in the first week to 12% in the second week. An interesting feature was then a rise, till, in the fourth week, his positives reached the high figure of 28%. This apparent progressive loss of immunity in serum treated cases, if it be confirmed, is of obvious practical importance, but I have not attempted to collect the results of Dick tests in a series of serum treated cases for the following reasons:

(1) If one is selecting only sharp cases for serum treatment, the reactions in these cases will obviously not be comparable with the non-serum group.

(2) With the mild type of scarlatina prevailing in Edinburgh such serum cases would have formed a relatively small group.

(3) It is now generally realised that antitoxic serum, if it is to be given at all, should be given at the earliest possible moment, and its influence negatives /

negatives any interpretation which one may place on the result of the test.

For these reasons I have not been able to study the behaviour of the reaction in the severe type of case. The possible influence which this unavoidable exclusion of severe cases may have on the results will be considered later.

## RESULTS

### TABLE I.

| Age in years | 0-1 | 1-5 | 6-10 | 11-15 | 16-20 | 21-30 | 31-40 | Total cases |
|---|---|---|---|---|---|---|---|---|
| Males | 0 | 27 | 36 | 7 | 7 | 4 | 3 | 84 |
| Females | 0 | 25 | 32 | 6 | 4 | 8 | 1 | 76 |
| Total cases. | 0 | 52 | 68 | 13 | 11 | 12 | 4 | 160 |

Table I shows the age and sex distribution of the 160 cases.

In the following pages will be found an Abstract of the case records.

Every patient in the series was suffering from mild scarlet fever. There were therefore only minor variations in the clinical picture, and these could not be found to correspond with the variations in the skin reaction. Clinical remarks have therefore been reduced to a minimum.

In place of the actual readings (the two greatest diameters at right angles to each other) I have substituted a mean diameter. The changes in this /

this from week to week will be found along with the age of the patient and day of disease on admission.

The cases have been numbered purely for purposes of reference, and are not in chronological order. Those in which the first week reading was in doubt have been placed at the end.

This Abstract is followed by TABLE 2 giving a summary of the results in each week of the disease.

## Abstract of Cases.

| No. | Name. | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|
| 1. | Evelyn C. | 6 | 4 | 27 | 30 | 25 | 0 | |
| 2. | John McD. | 6 | 2 | 0 | 0 | 0 | 0 | |
| 3. | Thos. W. | 9 | 4 | 18 | 0 | 0 | 0 | |
| 4. | James G. | 9 | 3 | 26 | 23 | 0 | 0 | |
| 5. | James S. | 7 | 4 | 28 | 22 | 0 | 0 | |
| 6. | Thos. J. | 8 | 2 | 18 | 0 | 0 | 0 | |
| 7. | Lizzie C. | 11 | 4 | 24 | 15 | 10 | 0 | |
| 8. | Ernest P. | 9 | 3 | 25 | 18 | 0 | 10 | Good scarlet. (see page 52.) |
| 9. | John W. | 8 | 3 | 18 | 0 | 0 | 0 | |
| 10. | Thos. L. | 3 | 3 | 18 | 10 | 0 | 0 | |
| 11. | Anna B. | 2 | 3 | 25 | 22 | 18 | 19 | Relapse in 5th week. Schultz-Charlton 50x40mm. |
| 12. | James M. | 10 | 4 | 0 | 0 | 0 | 0 | Typical scarlet. Rash bright, red tongue. |
| 13. | Maisie I. | 5 | 4 | 0 | 0 | 0 | 0 | Faint rash, tongue typical. |
| 14. | Duncan R. | 7 | 4 | 0 | 0 | 0 | 0 | Rash v.ft. Red strawberry tongue. |
| 15. | John D. | 5 | 4 | 20 | 0 | 0 | 0 | |
| 16. | Isa. D. | 3 | 3 | 20 | 0 | 0 | 0 | |
| 17. | Cath. T. | 3 | 4 | 20 | 12 | 0 | 0 | |
| 18. | Fanny G. | 6 | 2 | 18 | 0 | 0 | 0 | |
| 19. | Etta S. | 9 | 4 | 22 | 0 | 0 | 0 | |

| No. | Name | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|
| 20. | Nita A. | 5 | 2 | 22 | 0 | 0 | 0 | |
| 21. | John F. | 7 | 4 | 22 | 0 | 0 | 0 | |
| 22. | Mrs A. | 30 | 3 | 25 | 0 | 0 | 0 | |
| 23. | Ian McL. | 5 | 3 | 18 | 0 | 0 | 0 | |
| 24. | Greta O. | 6 | 3 | 18 | 0 | 0 | 0 | |
| 25. | Gordon S. | 4 | 2 | 16 | 16 | 0 | 0 | |
| 26. | James M. | 13 | 3 | 18 | 18 | 0 | 0 | |
| 27. | John R. | 4 | 2 | 18 | 0 | 0 | 0 | |
| 28. | Ellen D. | 6 | 4 | 0 | 0 | 0 | 0 | V. ft. erythema, tongue and throat typical. |
| 29. | Muriel A. | 8 | 2 | 25 | 0 | 0 | 0 | |
| 30. | James B. | 6 | 4 | 18 | 18 | 16 | 0 | |
| 31. | Peter H. | 5 | 4 | 15 | 12 | 17 | 0 | |
| 32. | Effie H. | 5 | 4 | 0 | 0 | 0 | 0 | Fading rash, red tongue and throat. |
| 33. | James C. | 5 | 2 | 0 | 0 | 0 | 0 | Good scarlet. |
| 34. | Annie O. | 13 | 2 | 18 | 0 | 0 | 0 | |
| 35. | Mrs A. | 24 | 3 | 30 | 16 | 20 | 0 | |
| 36. | Henry O. | 5 | 4 | 25 | 22 | 21 | 0 | |
| 37. | John D. | 6 | 2 | 18 | 0 | 0 | 0 | |
| 38. | Cath. B. | 5 | 2 | 18 | 0 | 0 | 0 | |
| 39. | Wm. E. | 8 | 3 | 28 | 0 | 0 | 0 | |
| 40. | Annie T. | 21 | 3 | 18 | 0 | 0 | 0 | |
| 41. | Alex. R. | 19 | 4 | 16 | 0 | 0 | 0 | |
| 42. | Thos. D. | 3 | 2 | 22 | 18 | 22 | 0 | |

| No. | Name. | Age. | Day of Admission. | Diameter in millimetres in each week. | | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 43. | Jean K. | 28 | 2 | 0 | 0 | 0 | 0 | | Faint rash, tongue atypical, red throat. |
| 44. | Helen M. | 7 | 2 | 28 | 22 | 25 | 0 | | |
| 45. | Betty D. | 10 | 2 | 26 | 0 | 0 | 0 | | |
| 46. | Ella M. | 8 | 4 | 0 | 0 | 0 | 0 | | Good scarlet. |
| 47. | Lena B. | 10 | 3 | 22 | 20 | 0 | 0 | | |
| 48. | Mary L. | 5 | 1 | 18 | 0 | 0 | 0 | | |
| 49. | Nancy S. | 10 | 3 | 20 | 0 | 0 | 0 | | |
| 50. | Wm. M. | 17 | 1 | 18 | 0 | 0 | 0 | | |
| 51. | Doug. R. | 34 | 2 | 25 | 0 | 0 | 0 | | |
| 52. | Sheila W. | 10 | 2 | 16 | 0 | 0 | 0 | | |
| 53. | Chris. D. | 9 | 3 | 0 | 0 | 0 | 0 | | Good scarlet. |
| 54. | Robt. A. | 12 | 2 | 0 | 0 | 0 | 0 | | Good scarlet. |
| 55. | Irene V. | 2 | 2 | 20 | 17 | 15 | 0 | 0 | |
| 56. | Betty C. | 18 | 2 | 20 | 0 | 0 | 0 | 0 | |
| 57. | Agnes S. | 4 | 3 | 18 | 0 | 0 | 0 | 0 | |
| 58. | Richd. B. | 8 | 3 | 26 | 0 | 0 | 0 | | |
| 59. | Michael D. | 14 | 4 | 27 | 0 | 0 | 0 | | |
| 60. | Wm. V. | 6 | 2 | 22 | 15 | 16 | 0 | 0 | |
| 61. | Mary L. | 4 | 3 | 23 | 0 | 0 | 0 | | |
| 62. | Mrs C. | 19 | 6 | 22 | 0 | 0 | 0 | | |
| 63. | Noel D. | 4 | 6 | 14 | 0 | 0 | 0 | 0 | |

| No. | Name. | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 64. | Wm. M. | 16 | 3 | 25 | 20 | 0 | 0 | 0 | Source of strain. S.2. |
| 65. | Eliz. L. | 21 | 3 | 21 | 21 | 15 | 24 | | Typical scarlet. |
| 66. | Thos. M. | 39 | 4 | 21 | 18 | 0 | 0 | | |
| 67. | Geo. P. | 8 | 4 | 18 | 0 | 0 | 0 | | |
| 68. | Anne R. | 6 | 2 | 32 | 22 | 21 | 0 | 0 | |
| 69. | Eric B. | 23 | 3 | 0 | 0 | 0 | 0 | 0 | Moderate rash, red throat. |
| 70. | John G. | 25 | 1 | 30 | 32 | 35 | 42 | 30 | Good scarlet. (see page 54.) |
| 71. | Geo. R. | 16 | 4 | 12 | 0 | 0 | 0 | | |
| 72. | Ina McE. | 13 | 7 | 25 | 0 | 0 | 0 | | |
| 73. | Thos M. | 9 | 2 | 32 | 0 | 0 | 0 | 0 | |
| 74. | Ian L. | 6 | 1 | 20 | 20 | 19 | 21 | | Good scarlet. |
| 75. | John N. | 5 | 2 | 14 | 12 | 0 | 0 | | |
| 76. | Bobby J. | 6 | 2 | 22 | 0 | 0 | 0 | | |
| 77. | John C. | 13 | 2 | 22 | 0 | 0 | 0 | | |
| 78. | Jackie P. | 1 | 7 | 18 | 12 | 0 | 0 | | |
| 79. | Chas. W. | 5 | 2 | 27 | 22 | 0 | 0 | | |
| 80. | Mrs F. | 24 | 4 | 21 | 0 | 0 | 0 | | |
| 81. | Ed. F. | 9 | 2 | 0 | 0 | 0 | 0 | 0 | Faint rash, tongue atypical. |
| 82. | Margt. H. | 6 | 2 | 22 | 0 | 0 | 0 | | |
| 83. | Lottie S. | 7 | 5 | 20 | 17 | 0 | 0 | | |
| 84. | Margt. R. | 6 | 3 | 18 | 0 | 0 | 0 | 0 | |

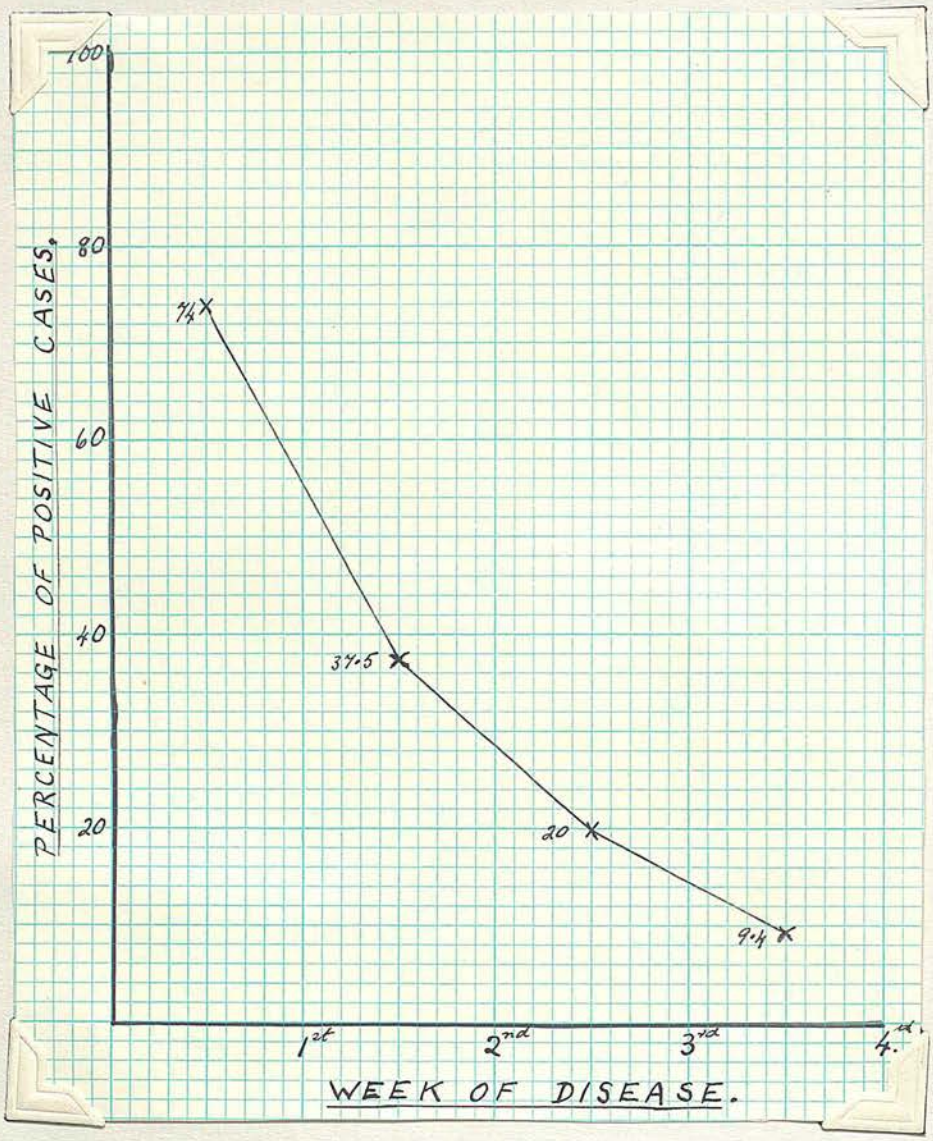
| No. | Name. | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | Remarks. |
|---|---|---|---|---|---|
| 85. | Hugh McL. | 23 | 2 | 0 0 0 0 | Good scarlet. |
| 86. | Alex. G. | 1 | 2 | 20 0 0 0 0 | |
| 87. | Rose F. | 8 | 3 | 21 0 0 0 0 | |
| 88. | Isobel B. | 16 | 3 | 20 0 0 0 0 | |
| 89. | Anne H. | 9 | 2 | 19 18 0 0 0 | |
| 90. | Hilda S. | 6 | 2 | 0 0 0 0 0 | Moderate rash, tongue atypical, dirty throat |
| 91. | Donald R. | 6 | 2 | 0 0 0 0 0 | Mod. rash, tongue atyp., dirty throat. |
| 92. | Oliver P. | 10 | 2 | 28 0 0 0 0 | |
| 93. | Betty H. | 11 | 4 | 28 20 19 17 0 | |
| 94. | Jackie H. | 7 | 4 | 22 0 20 0 0 0 | Good scarlet. (See page 52. ) |
| 95. | Anne R. | 4 | 2 | 18 14 10 0 | |
| 96. | Jean G. | 2 | 2 | 20 15 13 17 | V.ft. rash, tongue atyp., red throat. |
| 97. | Nora T. | 6 | 2 | 22 22 0 0 | |
| 98. | Sid. W. | 5 | 2 | 15 15 0 0 0 | |
| 99. | Kath. W. | 3 | 3 | 20 17 0 0 | |
| 100. | Allan C. | 2 | 2 | 19 17 16 14 14 | Good scarlet. |
| 101. | Ed. Smith | 16 | 4 | 22 0 0 0 | |
| 102. | Ronald T. | 10 | 2 | 0 0 0 0 | Good scarlet. |
| 103. | Geo. G. | 3 | 3 | 15 14 15 15 | Relapse in 5th week. |
| 104. | Anne W. | 4 | 3 | 0 0 0 0 0 | Faint rash, throat typical. |
| 105. | James S. | 2 | 2 | 0 0 0 0 0 | Mod. rash, throat typical. |

| No. | Name. | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 106. | Eliz. W. | 2 | 3 | 17 | 13 | 12 | 0 | 0 | |
| 107. | Billy B. | 5 | 2 | 20 | 15 | 0 | 0 | | |
| 108. | Wm. C. | 3 | 2 | 15 | 10 | 10 | 10 | | Good scarlet. |
| 109. | Ian S. | 6 | 2 | 15 | 10 | 15 | 15 | | Mod. rash, dirty throat. |
| 110. | Mrs J. | 34 | 3 | 25 | 0 | 0 | 0 | | |
| 111. | Logan M. | 4 | 2 | 20 | 20 | 0 | 0 | | |
| 112. | Thos. M. | 4 | 2 | 10 | 0 | 0 | 0 | 15 | (See page 52.) |
| 113. | Alex. B. | 8 | 3 | 19 | 17 | 0 | 0 | 0 | |
| 114. | Wm. F. | 8 | 3 | 0 | 0 | 0 | 0 | | Good scarlet. |
| 115. | Chas. J. | 7 | 2 | 19 | 10 | 0 | 0 | 0 | |
| 116. | Ken. E. | 5 | 6 | 15 | 15 | 0 | 0 | 0 | |
| 117. | Diana H. | 5 | 3 | 20 | 20 | 15 | 0 | 0 | |
| 118. | Eliz. B. | 5 | 4 | 28 | 28 | 22 | 24 | | Good scarlet. |
| 119. | Eliz. E. | 6 | 4 | 22 | 18 | 0 | 0 | | |
| 120. | Janet F. | 6 | 2 | 0 | 0 | 0 | 0 | | Faint rash, red throat. |
| 121. | Chris. M. | 3 | 2 | 10 | 16 | 0 | 0 | | |
| 122. | David L. | 7 | 2 | 0 | 0 | 0 | 0 | | Faint rash, red throat. |
| 123. | Margt. B. | 10 | 2 | 22 | 0 | 0 | 0 | | |
| 124. | Eliz. L. | 7 | 3 | 20 | 18 | 17 | 0 | | |
| 125. | Margt. J. | 8 | 3 | 24 | 19 | 17 | 0 | | |
| 126. | Wm. L. | 9 | 2 | 0 | 0 | 0 | 0 | | Mod. rash, tongue atyp. red throat. |
| 127. | Mary M. | 2 | 4 | 15 | 0 | 0 | 0 | | |

| No. | Name. | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | | | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|
| 128. | John G. | 34 | 7 | 0 | 0 | 0 | 0 | | | Good scarlet. |
| 129. | Robt. L. | 15 | 2 | 16 | 0 | 0 | 0 | | | |
| 130. | Geo. C. | 5 | 2 | 0 | 0 | 0 | 0 | | | Mod. rash, dirty throat. |
| 131. | Mary P. | 14 | 3 | 0 | 0 | 0 | 0 | | | Good scarlet. |
| 132. | John K. | 8 | 2 | 16 | 0 | 0 | 0 | | | |
| 133. | Ernest H. | 1 | 2 | 15 | 0 | 0 | 0 | | | |
| 134. | Muriel B. | 10 | 4 | 0 | 0 | 0 | 0 | | | Fading rash, tongue and throat typ. |
| 135. | Ian H. | 20 | 2 | 10 | 10 | 0 | 0 | | | |
| 136. | Janet C. | 4 | 2 | 19 | 0 | 0 | 0 | | | |
| 137. | Doris K. | 3 | 2 | 16 | 0 | 0 | 0 | | | |
| 138. | Robt. C. | 5 | 1 | 18 | 0 | 0 | 0 | | | |
| 139. | Geo. W. | 7 | 4 | 0 | 0 | 0 | 0 | | | Fading rash, tongue and throat typ. |
| 140, | Irene C. | 7 | 3 | 20 | 0 | 0 | 0 | | | |
| 141. | Denis H. | 11 | 2 | 18 | 0 | 0 | 0 | 0 | 0 | |
| 142. | Margt. T. | 17 | 4 | 24 | 15 | 0 | 0 | | | |
| 143. | John J. | 7 | 4 | 25 | 20 | 22 | 22 | | | Good scarlet. |
| 144. | Doris D. | 27 | 3 | 26 | 22 | 0 | 0 | 0 | | |
| 145. | Cath. G. | 3 | 1 | 15 | 0 | 0 | 0 | 0 | 0 | |
| 146. | Allan B. | 7 | 2 | 0 | 0 | 0 | 0 | | | Mod. rash, throat typ. |
| 147. | Margt. M. | 6 | 2 | 18 | 20 | 0 | 0 | | | |
| 148. | Eliz. W. | 3 | 2 | 0 | 0 | 0 | 0 | 0 | | Mod. rash, tongue atyp. red throat. |

| No. | Name. | Age. | Day of Admis: :sion. | Diameter in millimetres in each week. | | | | | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 149. | Wm. G. | 21 | 2 | 0 | 0 | 0 | 0 | 0 | Faint rash, tongue atyp. , red throat. |
| 150. | Betty H. | 4 | 4 | 0 | 0 | 0 | 0 | 0 | Fading rash, rasp. tongue, red throat. |
| 151. | And. C. | 10 | 2 | ? | 0 | 0 | 0 | 0 | Rash v. bright. |
| 152. | Minnie S. | 21 | 3 | ? | 0 | 0 | 0 | | Rash v. bright. |
| 153. | Cath. C. | 16 | 2 | ? | 0 | 0 | 0 | | Typical scarlet, rash v. bright. |
| 154. | Ronald D. | 6 | 3 | ? | 0 | 0 | 0 | 0 | Rash v. bright. |
| 155. | Mary L. | 11 | 3 | ? | 17 | 10 | 0 | 0 | Rash v. bright . |
| 156. | Donald J. | 3 | 2 | ? | 0 | 0 | 0 | | Rash v. bright . |
| 157. | Nancy H. | 8 | 3 | ? | 0 | 0 | 0 | | Typical scarlet, intense rash. |
| 158. | John W. | 6 | 4 | ? | 15 | 10 | 14 | | Rash still bright. |
| 159. | Lilias S. | 7 | 2 | ? | 15 | 15 | 10 | 0 | Typical scarlet, rash v. bright . |
| 160. | John H. | 15 | 2 | ? | 0 | 0 | 0 | | Typical scarlet, intense rash. |

GRAPH 1.




(Showing percentage positive in each week of the disease.)

TABLE 2.

(Showing summary of results in each week of disease)

| Week of Test | No. of cases tested. | Negative No. | Negative percent. | Positive No. | Positive percent. |
|---|---|---|---|---|---|
| 1st week | 160 | 42 | 26 | 118 | 74 |
| 2nd week | 160 | 100 | 62.5 | 60 | 37.5 |
| 3rd week | 160 | 128 | 80 | 32 | 20 |
| 4th week | 160 | 145 | 90.6 | 15 | 9.4 |
| 5th week | 44 | 39 | 89.6 | 5 | 11.4 |
| 6th week | 5 | 5 | 100 | | |

In the above table and accompanying graph are the results in each week of the disease in summary form.

Comment.

The figures for the fifth week are not strictly comparable with those for the first four weeks. Their interpretation will be considered later.

The results in the sixth week are too few to be of any significance.

Effect of Age on the Reaction.

TABLE 3.

| Group | No. in group | 1st week. Pos. | Neg. | 2nd week Pos. | Neg. | 3rd week Pos. | Neg. | 4th week Pos. | Neg. |
|---|---|---|---|---|---|---|---|---|---|
| 1-5 | 52 | 43 | 9 | 25 | 27 | 13 | 39 | 6 | 46 |
| 6-10 | 68 | 46 | 22 | 23 | 45 | 13 | 55 | 6 | 62 |
| 11-15 | 13 | 9 | 4 | 4 | 9 | 3 | 10 | 1 | 12 |
| 16-20 | 11 | 10 | 1 | 3 | 8 | 0 | 11 | 0 | 11 |
| 21-30 | 12 | 7 | 5 | 4 | 8 | 3 | 9 | 2 | 10 |
| 31-40 | 4 | 3 | 1 | 1 | 3 | 0 | 4 | 0 | 4 |
| Totals | 160 | 118 | 42 | 60 | 100 | 32 | 128 | 15 | 145 |

Table 3 shows the results obtained in each week of the disease in each age group. The first two groups furnish an interesting comparison.

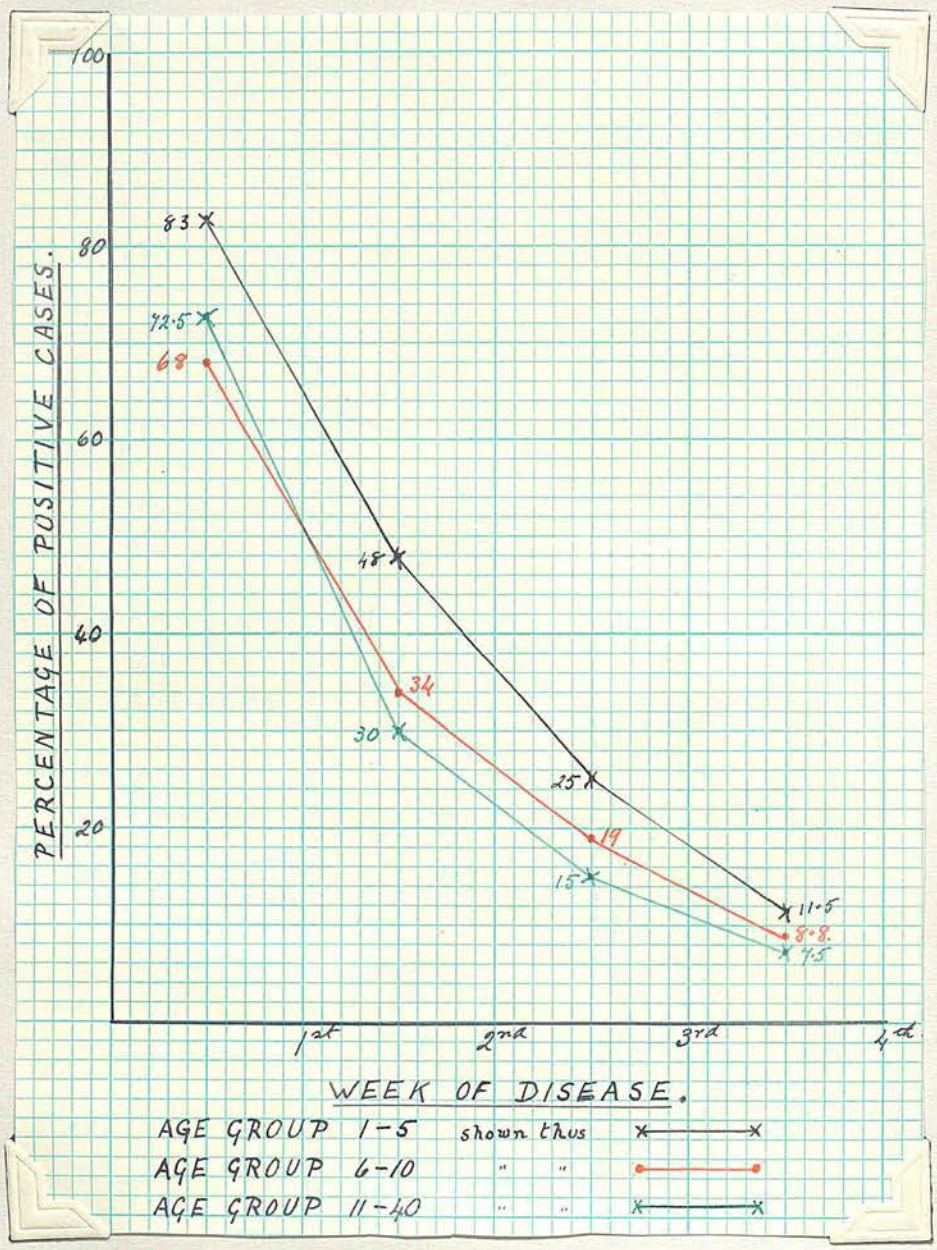
Group 1-5 - In the first week the predominance of positives over negatives is clearly defined. In the second week the positives and negatives about balance each other.

Group 6-10. Here the predominance of early positives is less evident, about one-third of the patients being negative in the first week. In the second week there is now a clear predominance of negatives, only about one-third of the patients retaining their positive reaction.

Lastly, it may be noted that in the 3rd and 4th weeks the actual number of positives recorded in the two groups are identical despite a considerable disparity in the size of the two groups.

According to these figures the change from a positive to a negative reaction would appear to occur less readily in young children.

GRAPH 2.




(Showing percentage positive in each age group.)

The effect of age on the change in the reaction can also be seen in Table 4 and the accompanying graph.

TABLE 4.

| Age Group | Total Cases | 1st week. No. Pos. | 1st week. Per cent. | 2nd week No. Pos. | 2nd week Per cent. | 3rd week No. Pos. | 3rd week Per cent. | 4th week No. Pos. | 4th week Per cent. |
|---|---|---|---|---|---|---|---|---|---|
| 1-5 | 52 | 43 | 83 | 25 | 48 | 13 | 25 | 6 | 11.5 |
| 6-10 | 68 | 46 | 68 | 23 | 34 | 13 | 19 | 6 | 8.8 |
| 11-40 | 40 | 29 | 72.5 | 12 | 30 | 6 | 15 | 3 | 7.5 |
| Totals | 160 | 118 | | 60 | | 32 | | 15 | |

All the cases over eleven years of age are considered together for comparisaon with the two earlier age groups and the results expressed as percentages.

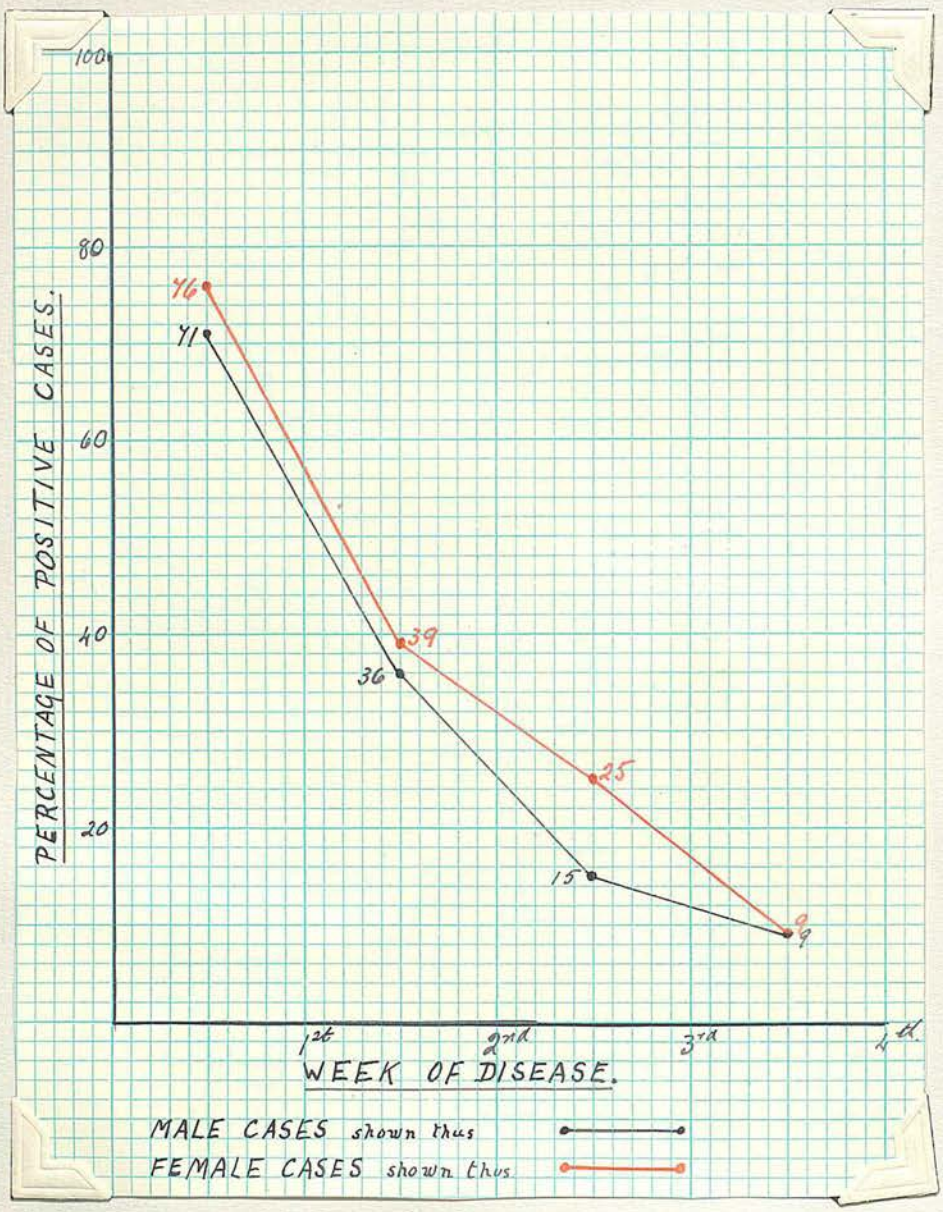
Comment.

(1) The change from positive to negative has usually taken place in the middle of the second week at all ages.

(2) This change is most clearly marked in the oldest age group.

(3) In each week the percentage of positives is highest in the youngest age group, in which there appears to be a "lag", most marked in the second week.

GRAPH 3.




(Showing percentage positive in both sexes.)

The Reaction in the two sexes.

TABLE 5.

| Sex. | Cases. | No. of positives in each week. 1st week. | 2nd week. | 3rd week. | 4th week. |
|---|---|---|---|---|---|
| Male. | 84 | 60 | 30 | 13 | 8 |
| Female | 76 | 58 | 30 | 19 | 7 |
| Totals | 160 | 118 | 60 | 32 | 15 |

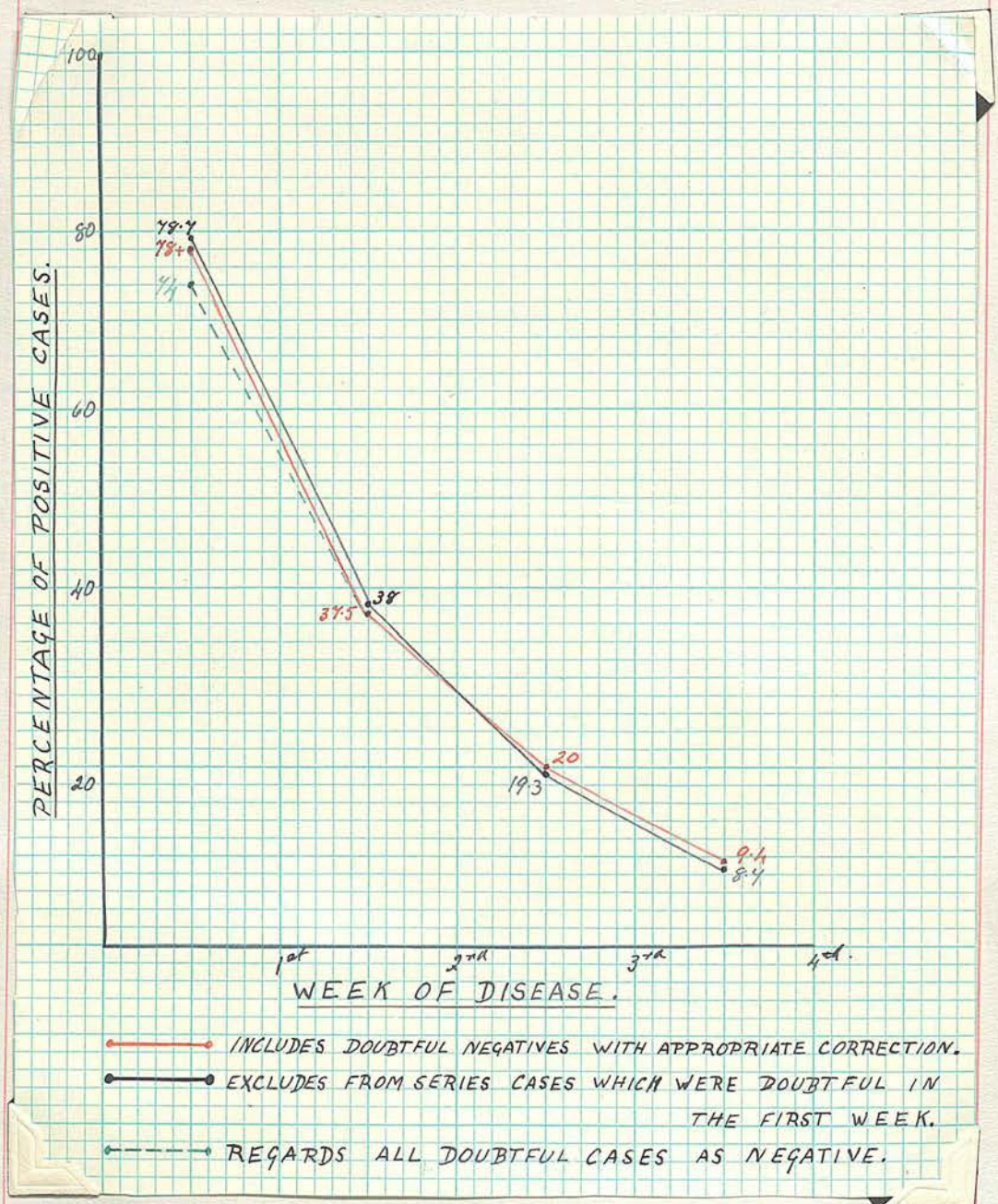
Table 5 shows the number of positive reactions obtained in each week of the disease distributed between the two sexes.

In the accompanying graph the results are expressed as positives percent.

Comment.

There appears to be no material difference between the sexes. The figures as they stand suggest a tendency to persistence of the Dick positive state in the female, but they are not large enough to warrant any definite conclusion.

GRAPH 4.




(Showing percentage positive with and without cases where the first week reading was doubtful.)

## Results in First Week.

The figure of 74% of positives in the acute stage is of interest for comparison with the results of previous workers, but is in at least one respect fallacious. In 10 of the 42 cases recorded as negative the rash was so intense, that a positive reaction may have been obscured. 3 of these cases were positive in the second week, and 2 of them were still positive by the fourth week. To obtain a more accurate figure one might either assume that at least 7 of these 10 first week negatives were positive or else exclude the whole 10 cases from the series.

TABLE 6.

| Weeks. | Including doubtful negatives. | | | Excluding doubtful negatives. | | |
|---|---|---|---|---|---|---|
| | No. tested. | Pos. | Pos. percent. | No. tested. | Pos. | Pos. percent. |
| 1 | 160 | 125* | 78.1 | 150 | 118 | 78.7 |
| 2 | 160 | 60 | 37.5 | 150 | 57 | 38.0 |
| 3 | 160 | 32 | 20.0 | 150 | 29 | 19.3 |
| 4 | 160 | 15 | 9.4 | 150 | 13 | 8.7 |

* Actual number positive 118. Add 7 doubtful cases.

Comment. 78% is more accurate than 74% for the first week figure. Thereafter the inclusion or exclusion of the doubtful cases produces no material change in the curve. (Graph 4.)

Day of Admission.

TABLE 7.

| Day of Disease. | No. of Cases Admitted. | Positive Reactions. | Percentage Positive. |
|---|---|---|---|
| 1 | 6 | 6 | |
| 2 | 70 | 48 | 71 up till 2nd day. |
| 3 | 42 | 33 | 79 on 3rd day. |
| 4 | 35 | 25 | |
| 5 | 1 | 1 | |
| 6 | 3 | 3 | 74 from 4th day on. |
| 7 | 3 | 2 | |
| Total | 160 | 118 | 74 in 1st week. |

Table 7 shows the 160 cases analysed according to the day of disease on admission, that is, the day on which the test was performed. The numbers admitted before the second and after the fourth day are too small to be considered separately.

TABLE 8.

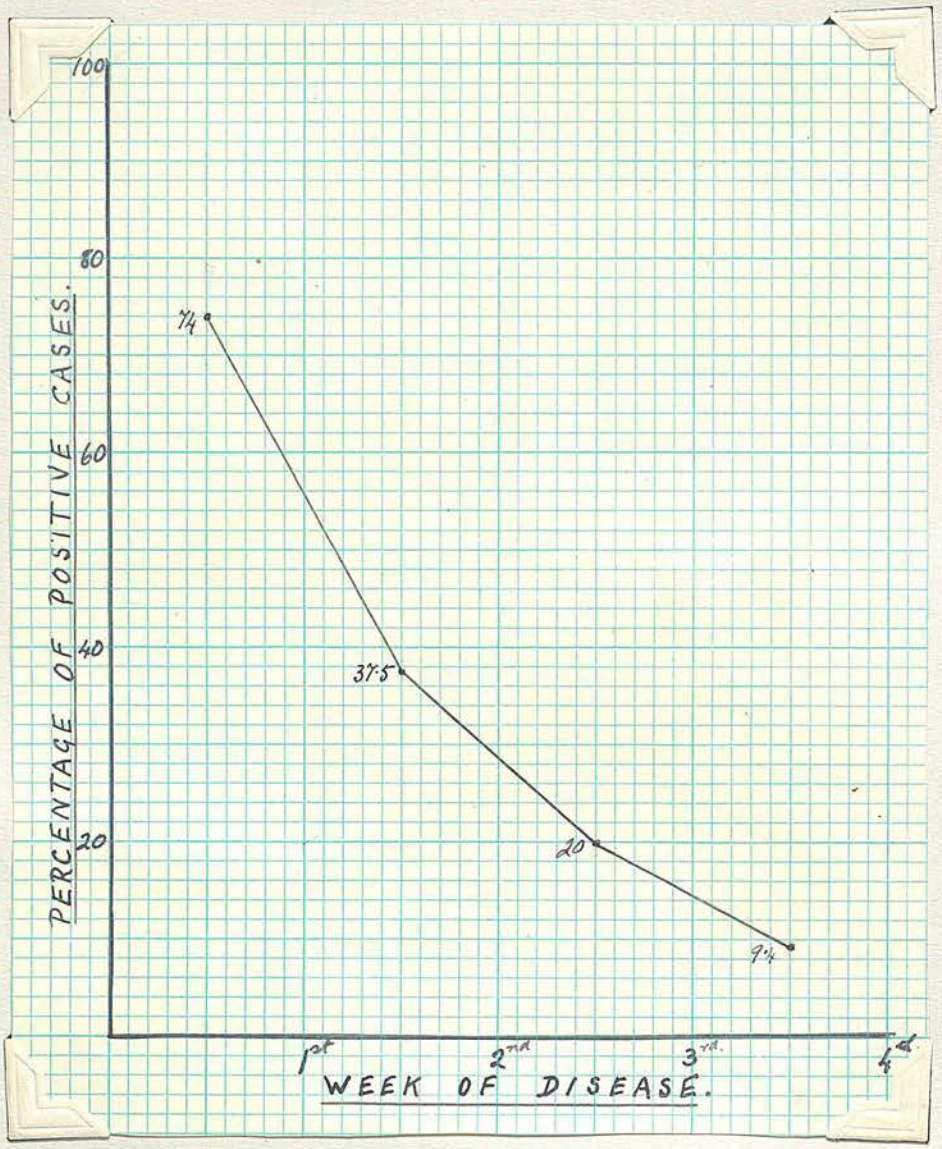
| Day of Disease. | No. of Cases Admitted. | Pos. | Doubtful Reactions. | Percentage pos. including doubtful reactions. |
|---|---|---|---|---|
| 1-2 | 76 | 54 | 5 | 78 |
| 3 | 42 | 33 | 4 | 88 |
| 4 -7 | 42 | 31 | 1 | 74 |

Table 5 shows the percentage of positives obtained during the different periods of the first week if the 10 cases with an intense rash are assumed to have been masked positives.

Comment.

The relatively high figure on the 3rd day is within the limits of the probable error and cannot be held to be significant. The figures can only be held to show that a considerable percentage of negative results may be obtained at a very early stage of the disease, which is in agreement with the majority of previous observers.

GRAPH 5.




(Showing percentage positive in each week of the disease.)

Changes in the Reaction during the Illness.

The percentage of positive reactors decreases in each week, the fall being sharpest between the first and second test - so that by the end of the first ten days of the illness there are only about a third of the cases giving positive reactions. In the third week only a fifth are still positive.

Of 118 cases recorded as positive in the first test, 61 were negative in the second test, but 3 cases were now showing up as positive. These 3 reactions were presumably masked in the first week due to the intensity of the rash (See Abstract). Of the 60 cases positive in the second week, 29 changed to negative in the third week, but one negative became positive (Case 94).

Of the 32 cases positive in the third week, 18 became negative but one other became positive (Case 8). This left 15 positive cases in the fourth week of the disease. Neglecting negative cases, of the original 118 cases taken as positive, 105 were negative in the fourth week, i,e. 89% of cases showed the change from positive to negative which is characteristic of the disease.

If reference is made to the Abstract it will be /

be seen that not only is there a progressive decrease in the number of positives each week, but the size of the reaction usually tends to get gradually smaller. In other cases it would appear that the reaction suddenly changes after perhaps three weeks to a "dead negative." In almost all such cases there has been a qualitative change in the preceding weeks, so that the change has not been so abrupt as it would appear on paper. This progressive decrease in intensity from week to week is highly characteristic, and is probably more significant than a minor variation in size, which, in a proportion of cases, may be due to mechanical error.

Unexpected fluctuations in size of the readings from week to week were singularly few. Nor were there unexpected qualitative changes, except that in some instances the reaction appeared stronger in the second week than it had been in the first. This was the type of case which changed slowly or not at all. On the other hand a faint reaction in the second week had almost invariably entirely disappeared by the third week.

Three cases appeared to change from negative to positive:-

| Case No. | Name. | Age. | 1st week | 2nd week | 3rd week | 4th week | 5th week | 6th week |
|---|---|---|---|---|---|---|---|---|
| 94 | Jack H. | 7 | 27x17 | 0x0 | 25x15 (faint) | 0x0 | 0x0 | 0x0 |
| 112 | Thos.N. | 4 | 10x10 (faint) | 0x0 | 0x0 | 0x0 | 15x15 (faint) | - |
| 8 | ErnestP. | 9 | 30x20 | 20x15 | 0x0 | 10x10 (faint) | | |

The first of these cases showed the apparent reappearance of a positive reaction in the course of the disease. Such variations in the reaction have been described by Lichtenstein (56) and this case may be an example of this phenomenon. On the other hand it is perhaps more likely that a positive reaction in the second week has been erroneously recorded as negative.

The second case is of interest for two reasons. The child contracted mild scarlet fever following diphtheria. Prior to the onset of the disease /

disease it was Dick tested according to routine in the diphtheria ward, and was apparently at that time a "Good positive" (unfortunately no actual measurements were recorded.) Retested on the second day of illness, and read 24 hours later, there was a faint but quite definite erythema. This, however, now measured only 10 mm. in both diameters - a minimal reaction. The rash, which had never been bright, had almost entirely faded, and there was no difficulty about deciding that the child was s till positive, but a very weak positive. Although careful search was made, no reappearance of the previous test, as has been recorded by Toomey (80) was noticed, nor, on the other hand, could there be found any area of pallor as Zingher (83) described. In the second week the reaction was "dead negative", and remained so till in the 5th week a faint but undoubted positive reaction reappeared. This was the last test prior to discharge. In 1924 Zingher (83) recorded that three children had become Dick positive again in t he 5th week of the disease.

The third case resembles the above in that it shows the apparent reappearance of the Dick positive state in convalescence, but as in the first case, this might be ascribed to the missing of a faint positive the previous week.

## Results in Convalescence.

In the fourth week the following 15 cases were still positive:

| No. | Name | Age. | 1st week | 2nd week | 3rd week | 4th week | 5th week |
|---|---|---|---|---|---|---|---|
| 1 | Betty H. | 11 | 28 | 20 | 19 | 17 | 0 |
| 2 | Lilian S. | 7 | ?0 | 15 | 15 | 10 | 0 |
| 3 | Ernest P. | 9 | 25 | 18 | ?0 | 10 | |
| 4 | Wm. C. | 3 | 15 | 10 | 10 | 10 | |
| 5 | Annie B. | 2 | 25 | 22 | 18 | 19 | Relapse |
| 6 | Geo. S. | 3 | 15 | 14 | 15 | 15 | Relapse |
| 7 | Allan C. | 2 | 19 | 17 | 16 | 14 | 14 |
| 8 | John G. | 25 | 30 | 32 | 35 | 42 | 30 |
| 9 | Eliz. L. | 21 | 21 | 21 | 15 | 24 | |
| 10 | Ian L. | 6 | 20 | 20 | 19 | 21 | |
| 11 | Jan G. | 2 | 20 | 15 | 13 | 17 | |
| 12 | Ian S. | 6 | 15 | 10 | 15 | 15 | |
| 13 | John W. | 6 | ?0 | 15 | 10 | 14 | |
| 14 | Joan J. | 7 | 25 | 20 | 22 | 22 | |
| 15 | Eliz. B. | 5 | 28 | 28 | 22 | 24 | |

Comment.

The first two cases were giving decreasing reactions each week and by the 5th week were "dead negative".

The next two cases were probably in the same category though there is considerable uncertainty about Case (3) owing to the the doubt about the accuracy of the 3rd week reading.

The next eleven cases were showing no evidence of becoming negative:-

Cases (5) and (6) relapsed in the fifth week. Antitoxic serum was given and the reaction became negative.

Cases (7) and (8) were still positive in the fifth week and had not relapsed.

Cases 9-15 were discharged in the fifth week prior to testing having shown no material change in reaction at any stage of the illness.

Cases 8 and 15, an adult and a child, have been retested after the elapse of about a year. Both are still giving strong positive reactions the test in the control arm being still quite negative.

## Summary of Results.

1. About one-fourth of the cases in this series of 160 patients suffering from scarlet fever appeared to be Dick negative in the acute stage of the disease.
2. This Dick negative state may occur in the earliest days of the illness.
3. Some of these negatives were due to the obscuring of the reaction by a vivid rash, but the majority could not be so explained.
4. Throughout the illness there was a progressive decrease in the number of positives till in the middle of the second week nearly two-thirds, and by the middle of the fourth week nine-tenths of the total cases, were negative.
5. Of the cases still positive in the fourth week a certain proportion were apparently approaching a Dick negative state, and some of these were negative the following week.
6. About 90% of the original positives showed this characteristic loss of the Dick positive state.
7. From a study of these cases, this change appears to occur less readily in young children.
8. Sex /

8. Sex cannot be held to be a factor of any importance.
9. Fluctuations between negative and positive in the course of the illness are very uncommon, if indeed they occur at all.
10. Occasionally the Dick positive state may reappear in convalescence.
11. Some 10% (or 7% of the total cases) failed to show any such change. Of these 11 cases 2 relapsed. In the other 149 cases no relapses occurred.
12. Pseudo-reactions were very seldom noted. Owing to the difficulty of their interpretation no such cases have been included in this series. They will be considered separately.

## DISCUSSION.

The methods adopted in this part of the thesis have been described, and the results presented and summarised. These results in themselves do not call for any lengthy discussion. In the first week 74% of the cases were positive. This figure shows a close conformity with the 75% recorded by Lichtenstein (56) over 450 cases, and 76% by Toyoda (81) over 1200 cases.

I should like to refer once again to the results obtained by the late Dr. Ker (50) in the Edinburgh City Hospital eight years ago. The figures which he recorded at that time were 74% positive of 23 cases in the first 3 days of the illness, and 9% positive of 44 cases in the fourth week. It is of course true that his 74% is not strictly comparable with the present 74% which includes cases admitted up to the end of the first week, but the fourth week figures do seem comparable, and it is interesting that the figures both at the beginning and the end of the illness should coincide so exactly. Some workers have obtained higher figures, others have obtained lower figures. These discrepancies have already been referred to, and from the experience gained in the present /

present study I am convinced that they will continue. The important question is - do they form a sufficient or reasonable basis for disputing the validity of the test? In my opinion they do not.

How do these discrepancies arise?

The Toxin.

The uniformity in strength of the toxin used is of primary importance. (58) Lorenz and Nobel tested three "standard" toxins from Vienna, Marburg, and America in 100 children and obtained variations of as much as 33% in the results. They concluded rightly that some uniform method of preparation and standardisation of toxin would be an essential for further investigations. One might add that if variation in toxin is of such importance in testing healthy children it becomes a factor of even greater importance in testing persons in the course of the disease itself. Brown (12) in 1925 showed that a marked difference could be found in results both in the acute and convalescent stages by using toxins of different strength.

Interpretation of "Positives."

In 1928 Burton and Balmain (13) reported

90.5% /

90.5% of positives in the first 3 days, but of these, 49% had a reaction of from only quarter to half an inch in diameter. Most workers have adopted an erythema of 10 mm. in both diameters as a minimal standard, and so their figure of 90% has at once to be reduced. This illustrates the factor of size.

Johan (47) in 1927 reported the result of 17,000 Dick tests. He laid particular stress on the importance of recording the positives as strong, moderate, or weak positives. Of 1000 positives obtained by one observer in one town almost 50% were "weak positives" - an erythema of 10-20 mm. Even in health Johan admitted the difficulty of drawing a line between "weak positives" and "negatives", and this becomes an obvious source of error when the results of individual observers come to be compared.

In 1924 Zingher (83) said that a really strong positive reaction in the acute stage of the illness spoke strongly against the diagnosis of scarlet fever. In my experience this conclusion is amply justified. Reactions of fair size are sometimes met with, but I have never seen what I would describe as a "brilliant" positive in a case of scarlet fever. That persons with this brilliant type /

type of reaction do frequently contract scarlet fever is certain. Some loss of intensity apparently occurs in the earliest stage of the disease. When a person with a moderate or weak positive reaction takes scarlet fever, the reading of the Dick reaction in the midst of a generalised erythema may become a matter of considerable difficulty. In 10 of the recorded 160 cases it became an impossibility. Even in the absence of a bright rash, a weak but quite definite positive may be obscured by the observer unconsciously exerting slight pressure in a downward direction on the skin of the forearm, while extending the child's arm to read the reaction. It is better to keep the arm flexed with the wrist a little elevated, while a little gentle friction over the site of injection may make a very faint reaction easier to read. A casual glance at the two arms may enable one to interpret the Dick reaction correctly in health, but it will not do so in scarlet fever. It may seem unnecessary to stress this point, but I feel that some of the low figures in the literature may have been due to want of care in reading the reaction. As this care is necessary, it is obvious that if one has already decided that the Dick reaction is of no value /

value whatever, and one is not looking for positives, they will not be found. Conversely it does not take much imagination to stretch a negative into a positive.

In this matter of individual interpretation, the time at which the result is read, forms another source of discrepancy, and possibly of error. In the present work the results recorded have been obtained at the end of twenty-four hours, as this has been the practice of most observers, and for general purposes this is probably the most reliable as well as perhaps the most convenient practice. On the other hand the majority of reactions are fading at the end of twenty-four hours, and I am convinced that in scarlet fever an earlier reading would yield a higher percentage of positives.

The following case is of interest:

> Nurse T., aged 21. The patient had been nursing in a general hospital and was admitted with mild scarlet fever. While performing the test on the evening of admission I indicated to her in a few words the purpose of the test and what one might expect to find next day. Twenty-four hours later the result was clearly negative, the rash having almost disappeared. She volunteered the information, however, that "it had been red in the morning". A week later the test was repeated with the same result and the same story. Unfortunately an opportunity was not taken on these two occasions of retesting her immediately. In the third week, however, I returned at the end of 16 hours to find a faint but typical reaction of 25 x 20 mm. She displayed /

displayed no enthusiasm about it on this occasion, declaring that in the previous weeks 'it had been more red than that.' At the end of 24 hours, that is 8 hours later, the erythema was just perceptible, but too faint to measure. In the fourth week the reaction was quite negative.

Debré and Lamy (26) investigated 61 cases in the first 5 days of the disease. They found that only 33% were positive at the end of 24 hours, but if read at the end of four to five hours "9 out of 10" were positive.

Selection of Cases.

Any selection of cases must also inevitably affect the results. The series recorded here have all been moderate or mild cases. It is difficult to estimate to what extent the first week figures would have been affected had it been possible to include the sharp cases. I am inclined to think that it would not have materially altered the percentage of positives, but would have increased the number of doubtful cases, a fair number of which would probably have been positive in the second week, when the bright rash had faded. By counting these doubtful cases as positives a very high percentage might be obtained. It is impossible to say how the fourth week figure would have been affected by the inclusion of these sharper cases.

On /

On the other hand in an epidemic of severe scarlet fever with a relatively high proportion of septic and toxic cases the percentage of early positives might be lowered.

It is obvious, therefore, that the results of different workers in different parts of the world in different years can never be expected to coincide.

Finally, in regard to the unduly low figures which have appeared in the literature from time to time there is the possibility that cases have been included which have not been scarlet fever. A small child may be sent into hospital for observation with the history that it had a rash the day previously. The difficulty of deciding whether this is or is not a mild case of scarlet fever is only too well known to every worker in an Infectious Diseases hospital. And at the end of four weeks one may still be unable to come to a decision, or one's decision may be wrong. That the inclusion of non-scarlet cases will upset the results is obvious, but there is one type of case which needs special consideration in this connection.

It not infrequently happens that two or three children from one family are admitted to hospital /

hospital together, or within a few days of each other, all labelled "Scarlet Fever". One may be a definite case of scarlet fever, another may have a red throat with no sign of a rash, and a third may have nothing but a rather incomplete history of a sore throat perhaps seven days previously. The latter two cases present a difficult problem from more than one point of view. From the present aspect only, however, is it reasonable to regard these cases as scarlet fever? The child with the local infection and no rash will be, naturally enough, Dick negative, and the inclusion of such a case in a series of cases of "Scarlet Fever" is obviously unsound.

Case 136, Janet C.; aged 4, admitted on 2nd day of disease. 1st day scarlatiniform rash blanched by Antitoxin 1/10. Throat, typical scarlet. Tongue, "white strawberry."

| | | |
|---|---|---|
| Dick Tests | 1st week | 20 x 18 mm. |
| | 2nd " | 0 x 0 |
| | 3rd " | 0 x 0 |
| | 4th " | 0 x 0 |
| | 5th " | 0 x 0 |

The brother of this patient was admitted to hospital on the same day:-

Gordon C.; aged 9, admitted on 1st day of disease. Rash nil. Tonsils swollen and congested. Soft Palate Red. Tongue, not suggestive of scarlet fever.

Dick /

Dick Test 0 x 0 mm. each week.

The retention of such a term as "Scarlatina sine eruptione" is, I think, in the light of our present knowledge to be avoided. My contention at the moment, however, is, that it is absurd to regard such a case as one of scarlet fever, expect the Dick reaction to be positive, and then, when it is found to be negative, query the validity of the test.

Pseudo-Reactions.

Pseudo-reactions may sometimes form another source of error. The Dicks (31) in their original work used, as a control test, undiluted fluid from the culture medium. Zingher (83) advocated the use of toxin inactivated by heating at 100°C. for 1 hour. He believed that the proteins were not materially affected by the boiling process. Previously he had employed toxin-antitoxin mixtures, but found them unsatisfactory, as in some cases the serum appeared to produce some curious inhibitory action on the streptococcus protein, the reaction being interpreted wrongly as a "straight positive." In other cases he found a delayed reaction appearing at the site of the control injection in forty-eight hours. These fallacies, he declared, were all eliminated, if heated /

heated control was used. He described 4 distinct types of reaction.

(1) The "Positive" began in 4-6 hours, and reached a maximum in 24 hours.

(2) The "Negative" showed no change.

(3) The "Negative Pseudo", which showed areas of redness, similar in size and appearance at the site of test and control, due to the person being sensitive to the autolysed protein of the haemolytic streptococcus or to some protein constituent of the test fluid - such as horse or sheep serum, beef extract, peptone, etc., used for enriching the medium. Such a person he found to be immune to scarlet fever, their serum blanching a scarlatinal rash.

(4) The "Positive-combined" type of reaction showed more intensely on the test arm. The control arm showed a lesser degree of redness, but this varied "depending on the protein sensitiveness of different persons."

The Dicks (33) later stressed the importance of using strong toxins which could be diluted at least 1/1000, and the reducing of foreign proteins in the culture medium to a minimum.

The /

The actual frequency of Pseudo-reactions appears to vary greatly with the age of the persons tested.

Benson and Simpson[3] found that no less than 15.5% occurred amongst the nursing staff, whereas O'Brien and Okell[67] obtained only 5.2% of pseudo-reactions in 673 tests made at various ages.

As to the occurrence of these reactions in the course of scarlet fever, figures are difficult to obtain, but in 1925 Rosen and Korobicina[73] recorded that "pseudo-reactions in the scarlet fever patients were a very seldom occurrence." This certainly has been my experience. Only two such cases were met with in the present series and they have not been included owing to the difficulty of their interpretation.

Case Agnes R. (aged 12) mild scarlet fever, admitted on third day of illness.

1st week (day of admission) Dick = 20 x 15;
Control = 25 x 22
(repeated following day) Dick = 20 x 15;
Control = 35 x 18

The above readings were taken at the end of 24 hours. In both instances the reaction at the site of the control test exceeded in size and intensity the reaction at the site of the test /

test proper. The child was apparently Dick negative. At the end of 48 hours the control test had increased still further in size and intensity whereas the other reaction had faded. This early fading was suggestive of a true Dick reaction, and one was now not satisfied that the patient was really Dick negative. After two days' interval a retest with a different batch of toxin again produced a control test which exceeded in size and intensity the reaction on the test arm, and only reached its maximum at the end of 48 hours. If the child were Dick negative the reaction should have behaved similarly in both arms. If the child were Dick positive the Dick test should have exceeded the control test when read at 24 hours.

The subsequent readings were as follows:

| | Dick. | Control. |
|---|---|---|
| 3rd week | 21 x 14 (fading 24 hours) | 25 x 18 (increasing 24 hours) |
| 4th week | 23 x 17 (very faint) | 27 x 15 (increasing 24 hours) |
| 5th & 6th weeks | Not Tested. | |
| 7th week | 0 x 0 | 22 x 18 (increasing 24 hours). |

The interesting feature of this case is the fact that while on admission she appeared to be exhibiting a pseudo-negative type of reaction the subsequent fading of the test proper from week to week till it became negative suggests that she was really Dick positive from the commencement, this state being masked by a pseudo-reaction, which for some reason was disproportionately bright. In the light of this case Zingher's[83] original contention that /

that for the purpose of the test the proteins are unaffected by heat will have to be reconsidered.

Winnie L.; aged 6, mild scarlet fever, admitted on 4th day of disease. Throat and tongue typical. Rash:- punctiform element rather coarse, erythema a little patchy but blanched by Scarlet Antitoxin diluted 1/10.

| | Dick. | Control. |
|---|---|---|
| 1st week (day of admission) | 15 x 15 (brighter than control). | 15 x 15 |
| 2nd week | 20 x 15 | 12 x 10 |
| 3rd week | 20 x 10 | 10 x 10 (very faint) |
| 4th week | 28 x 14 | 0 x 0 |
| 15 months later | 30 x 25 | 0 x 0 |

This child was evidently a true Dick positive, and illustrates how the reaction may tend to be diminished in the early stage of the illness. Apparently no immunity was acquired during the course of the disease, and when the rash faded the reaction tended to increase again to what was presumably its usual level.

It has been described here, however, mainly to show that a control test may change from positive to negative so that a person may appear to present a "combined-positive" reaction at one occasion, and a "straight positive" at another. If the control reaction /

reaction were strong enough even a "pseudo-negative" might be recorded.

These two cases show that the interpretation of pseudo-reactions may present difficulty, and that if the tests be performed once only, there is a possibility of error arising. The first case suggests that the use of a heated fluid may cause such vivid reactions in certain individuals, as to render this method of control unreliable. The second case is of interest because it suggests that the reaction to the control fluid may be inconstant, and fluctuate from time to time in the same person. As to the actual worth of a control test there is some difference of opinion. Von Groer (41) believes it to be valueless and has dispensed with its use entirely. This represents an extreme view.

In my opinion the real nature of the pseudo-reaction is as yet so imperfectly understood that further study will be necessary before we are in a position to draw conclusions as to its value.

It may seem that I have dwelt unduly upon the sources of error which may arise in the interpretation of the Dick reaction, in health, and more particularly, in the disease itself. I have done /

done so because I feel that it is these errors which have singly or collectively given rise to disorder and confusion in the findings of individual workers, and this has formed the basis for much of the criticism, which has been directed against the validity of the test. There are, however, certain anomalies and difficulties which do appear to be more numerous in the case of the Dick test than in the case of the Schick test. These difficulties have, I think, been rather exaggerated, but must nevertheless be considered.

Why do Dick negative persons take Scarlet Fever?

Every now and again a person known to be Dick negative takes scarlet fever. To many writers it would appear that this has been an insuperable difficulty. When these cases are analysed one finds that many of them have occurred in members of a hospital staff. One should remember that the Dick test consists essentially in the introduction of an arbitrary amount of toxin into the skin, that amount having by previous experience proved itself to be a reliable index of immunity in the vast majority of cases. A nurse who has passed this test, which appears /

appears to be good enough for normal circumstances, develops scarlet fever, and it is almost invariably mild scarlet fever. Does that prove that the test is fallacious? Can the circumstances of a nurse exposed to massive doses of highly toxigenic streptococci be regarded as normal circumstances? In 1929 Dr. Benson (2) recorded the fact that of 290 Dick negative individuals, who subsequent to the application of the test were in intimate contact with scarlet fever for periods varying from weeks to years, only 2 had (at that time) contracted the disease. On the other hand no fewer than 41 out of 178 Dick positive reactors who had been similarly exposed developed scarlet fever.

As another example of its reliability one might quote a case of scarlet fever which appeared among 50 diphtheria convalescents. Of 37 who were Dick negative none developed the disease, while of 13 who were Dick positive 6 developed scarlet fever.

My contention is that the test has proved itself reliable for almost all conditions. The factors concerned in the establishment of any infection are multiple, and all these factors have to be remembered when an isolated instance of scarlatina in /

in a Dick negative individual is encountered. I have already referred to the numerous ways in which a person may be concluded to be Dick negative in error. The subsequent development of scarlatina in such a person helps to confuse the issue. There is one other possibility which, while it is little more than speculation, is intriguing.

I have already referred to an interesting paper by Lees in which no less than 11 Dick negative persons contracted scarlet fever. On performing the Schultz-Charlton test it was found that convalescent serum was more effective than scarlatinal antitoxin. Is it possible that this epidemic was due to a toxin different from the standard toxin and antitoxin used in testing? Is there any evidence that multiple toxins exist?

McLachlan (63) found that of 98 strains of haemolytic streptococci isolated from scarlet fever patients all produced a toxic principle, which, in high dilution, was capable of evoking a cutaneous reaction in susceptible persons. A certain proportion of haemolytic streptococci from other sources possessed a similar toxogenic property, and in /

in a few cases the toxin produced was equally active with that of the scarlatinal strain. He found that these might evoke cutaneous reactions both in known positive reactors and in persons who did not react to standard scarlatinal toxin. In some cases the antitoxic sera being used for treatment failed to neutralise either the scarlatinal toxins or those from the non-scarlet sources.

Griffith (40) found that 156 of 222 strains fell into 4 chief "serological types the properties of which would likely vary in different localities and in different outbreaks of scarlet fever in the same locality."

Smith (76) also found that strains from 210 cases of scarlet fever could be divided into several types, but that strains from non-scarlet sources and from normal throats might fall into these same types.

McLachlan and Mackie (64) found that there were certain groups which corresponded generally to the "types" described by Smith and by Griffith, but there was such considerable antigenic overlap among the different groups that the differentiation and relationship of strains could not be expressed satisfactorily by formulating definite serological types. /

types. A "Streptococcus Scarlatina" group could not be defined by serological methods.

In the meantime, therefore, we can only conclude that the existence of type specific toxins has not been established, but that there is some evidence that differences between toxins do exist. A study of these differences by using toxins from different sources, instead of the standard toxin, throughout the course of the disease, correlating the results with the strain of the infecting organism, may go far to explain some of the present difficulties, in particular the initial Dick negative and the late Dick positive.

Why are there so many Dick negatives early in the disease?

Apart from the occasional case of the Dick negative person who contracts scarlet fever, one is faced with the problem of why such a large percentage appear to be negative in the first few days. This percentage has varied greatly with different observers, and I have already indicated the reasons for this variation. Why is it that about one person in every four is negative at the first /

first test? Many explanations have been advanced, and it is usually concluded that "immunity is rapidly acquired." It seems to me that undue stress has been laid on these early Dick negatives. The rash varies widely in intensity from case to case. This variation depends on, firstly, the potency of what Okell (69) calls the "erythrogenic" toxin; secondly, the antitoxic content of the patient's blood; and last, but not least, a local factor. The nature of this local resistance is not understood, but local resistance and general resistance are not necessarily parallel. The rash which develops in each case may be regarded as the summation effect of those factors, and this response as a generalised Dick reaction using a toxin of variable potency. A local Dick test is then performed, usually when the general response is just reaching, or has just reached, its maximum. Is it surprising that in a proportion of cases the additional response to this local toxin is so feeble as to be imperceptible? The relatively insusceptible person has a poorly developed rash and a feeble Dick reaction, the highly susceptible person has an intense rash and the test tends to be obscured. The good positive and the "dead negative", which are the /

the two extremes, appear to me to be largely dependent on a disproportion between the potency of the erythrogenic toxin absorbed from the site of infection and the test toxin introduced at the site of infection.

The importance of the local factor is difficult to assess and the nature of the resistance difficult to understand. Further, the specificity of this resistance is open to doubt.

Zingher (83) noted in the midst of a scarlet fever rash an area of pallor corresponding to a previous Dick test. The pallid area, which he believed to be due to a local cellular immunity, was surrounded by a ring of intense erythema, due, he thought, to the sensitizing of cells which had not received enough toxin to produce immunity.

Toomey, (80) on the other hand, noted the reappearance of redness at the site of previous Dick tests in 15 out of 35 nurses, who subsequently developed scarlet fever a few weeks after testing. in 2 of these cases a whole year had elapsed. In no case did he note the blanching reported by Zingher.

If we accept Zingher's interpretation as being reasonable one may conclude that Toomey's toxin /

toxin was less potent. This conclusion is strengthened if we consider the results in a paper published by Brown.(12) This worker used a toxin diluted 1/6000 for testing, and noted the reappear:
:ance phenomenon in 6 cases. One case originally negative showed a faintly positive reaction when the scarlet fever rash appeared. On the other hand when using a toxin diluted 1/1000 the red ring appearance was noted in one out of 3 cases.

Moriwaki(66) also recorded the reappearance of a Dick test performed 21 days previously, but in 3 cases who developed scarlatina 7-14 days after the test, areas of blanching were observed. This suggests that the local immunity is a transient one.

Doubts as to the specificity of these reactions are cast by an interesting case, also described by Moriwaki, where a Dick reaction reappeared following the development of a staphylo:
:coccal infection of the thigh. A case of Toomey's(80) which developed measles showed the same phenomenon.

Ferry(36) has recorded the reappearance of a number of Dick tests in a positive reactor, aged 21, who was being used for the standardisation of toxin, when one week later the man contracted measles. The reactions /

reactions reappeared in similar size and intensity, and were clearly distinguished from the measles rash. They persisted for 24 hours and rapidly faded. It is interesting to note, however, that where a toxin-antitoxin mixture had been injected with an excess of antitoxin, no redness appeared. Unfortunately these interesting cases are seldom met with, as Dick testing is frequently followed by specific prophylaxis. In the present study only one case of the kind was encountered and no trace of either blanching or reddening could be found.

There may also be a nonspecific factor in the local resistance, which may help to play a part in the early assumption of the Dick negative state. Debré, Lamy, and Bonnet (28) found that in 4 children suffering from measles a positive reaction disappeared the day after the rash but reappeared in one month. In one infant an active erythema due to irradiations from a quartz lamp produced a temporary negative state.

Cooke (21) found that the skin susceptibility to scarlatinal toxin was greatly diminished during the acute stage of a measles infection but returned during convalescence.

The following are the results which I have obtained /

obtained on Dick testing 29 children suffering from measles in various stages of the disease. The age varied from 1 year to 10 years, the average age being 3½ years:-

Only 11 cases (31%) gave positive reactions whereas in that age group about 60% of positive reactions might have been expected, (Ker, McCartney and McGarrity)(50). Furthermore, not one strong positive reaction occurred. Three were of moderate strength (20-25 mm.). The other eight children gave feeble reactions.

In one case there was a history of previous scarlet fever. The reaction was negative.

From these results there would appear to be an increased resistance to Dick toxin during measles, and if we accept the Dick test as a reliable index of immunity then one may conclude that a child suffering from measles is relatively resistant to scarlet fever. If this be contrary to the facts then the test must stand condemned. It is, however, the case, that scarlatina is an uncommon complication of measles and tends to be mild in character. It is difficult to believe that this resistance to scarlet fever rests on any change in the antitoxin content of the blood. It /

It may be more easily explained by some non-specific change of sensitivity in the skin. This illustrates once again the importance of the local factor in the resistance to the toxin of the haemolytic streptococcus.

Does a Dick Positive Reaction always indicate susceptibility?

In a definite proportion of cases the Dick reaction does not become negative during the course of scarlet fever. The percentage positive in convalescence was stated by Okell and Parish[70] to be 18%. The amazingly high figure of 31% was reported by Peters and Allison[72]. I have already referred to their paper and I am unable to account for their results, assuming their toxin to be above reproach. An even higher figure (40%) was recorded by Ciuca, Balteanu and Toma[14], and is equally difficult to explain. These excessively high figures are not in keeping with the results of other workers, most of whom have recorded a much lower figure. Thus we find that of the 22 positive cases described by Okell and Parish, 8 were doubtful cases, which reduces their percentage to 12 instead of 18. Toyoda and his co-workers[81] over a very large series of cases /

cases found that 13.7% remained positive. Kinloch, Smith and Taylor (51) obtained 14% of positives in the fourth week over 158 cases, a series equal in size to that which has formed the basis of the present study. The late Dr. Ker's figure in the fourth week was 9% which corresponds with my own figure. I have already briefly analysed the 15 positive cases in the present series, and shown how, while 2 cases were approaching the Dick negative state, 11 cases were showing no change. The fact that 2 cases out of 15 relapsed, whereas there were no relapses amongst the other 145 cases, suggests that the persistance of the Dick positive state is of very definite significance. I have also suggested that this apparent failure or delay in the development of immunity is more often met with in young children. Harries and Macfarlane (43) also gained this impression in 1926. Can we assume that the other 11 cases are all liable to reinfection? Two cases which I have followed up are showing no change in the reaction a year later. Broadly speaking, Dick reactions and Schultz-Charlton reactions show a close correlation. Joe (46) proved this in 25 out of 27 cases. Debré, Lamy and Bonnet obtained blanching with 21 Dick negative sera. 13 Dick /

Dick positive controls failed. Only one of my cases was investigated from this point of view (Case 70). 0.5 cc. of his serum was injected intracutaneously into a good scarlatinal rash. No blanching resulted. A control test of 0.2 cc. of scarlatinal antitoxin diluted 1:10 produced good blanching.

Occasionally, however, the serum of a Dick positive convalescent gives a positive Schultz-Charlton test. Furthermore, while the morbidity among adults is very low, a fair percentage of the adult population are Dick positive reactors. According to Toyoda the figure is approximately 13% and some of these persons may also give a Schultz-Charlton positive (blanching) reaction.

Kondo (53) reported that 79% of 101 cases became Dick positive during the disease, though their serum gave blanching reactions. None of the other Japanese workers have produced these quite unusual findings, but Ando (1) has published a series of papers which, if they are confirmed, throw much light on this problem of the late Dick positive reactor. This worker maintains that ordinary Dick filtrate contains two active principles. The one produces the character:

:istic skin reaction in man, and is inactivated by heat /

heat at 80° for 30 minutes. Injection in large doses produces experimental scarlet fever in man. The other is apparently a bacterial nucleoprotein, and may be obtained by the partial solution of the sedimented bacterial bodies. This "Endotoxin" is heat stable at 100° for 2 hrs. and will not produce scarlatina in man, but produces allergic reactions in skin testing. Toyoda and his co-workers (81) have followed up the work of Ando and have tested some 1200 persons with

(1) Dick Filtrate.

(2) Heat stable toxin.

(3) Heat labile toxin.

They find that the population can be classified into 5 groups on the basis of these reactions.

| Group. | Dick Toxin. | Heat stable toxin. | Heat labile toxin. | Immunity |
|---|---|---|---|---|
| 1 | + | - | + | Nil. |
| 2 | + | + | + | Imperfect. |
| 3 | + | + | - | Good (with allergy) |
| 4 | - | + | - | do. |
| 5 | - | - | - | Very good (without allergy) |

In /

In conclusion they state that a study of these reactions "made them feel that the mysteries of the Dick Test previously unfathomable have now been perfectly solved."

In the second part of this study an account will be given of the results which I have obtained using a heat stable extract derived from the ground bodies of haemolytic streptococci. The results appear to show the development of an allergic reaction during the course of scarlet fever and are of interest in relation to the conclusions of these Japanese investigators.

The following cases are of interest in a consideration of the interpretation of a Dick positive reaction in scarlet fever.

Mary C., aged 6, admitted on 3rd day of illness with history of a rash the previous day. There was a faint erythema over the trunk which was not scarlatiniform in character. The tongue was not suggestive of scarlet fever. The Fauces were mildly congested. There was no sore throat, headache or vomiting. No pyrexia or rise of pulse rate.

1st week. The Dick test on admission produced the brilliant type of reaction, 42 mm. x 35 mm. with a surrounding flare. (I have never seen this type of reaction in a scarlet fever patient.) The control test was quite negative.

Second week. The test was repeated in the second week and /

and, in addition, 0.2 c.cm. of "Endotoxin" was also introduced intracutaneously. (The preparation and use of this type of extract will be described later. It is an extract obtained from the ground bodies of haemolytic streptococci.) The readings were:- Dick, 50 x 42 mm., Endotoxin, 40 x 30mm. The Dick test was still a brilliant positive and the Endotoxin was also producing a strong reaction, which is quite unusual till later in the disease.

Third week. In the third week the following neutralisation experiment was carried out. Five tubes were prepared according to the following table.

| Tube. | Antitoxin. | Saline. | Exotoxin 1/1000 | Endotoxin 1/100 |
|---|---|---|---|---|
| 1 | 0.1 cc. | - | 0.9 cc. | - |
| 2 | 0.1 cc. | - | - | 0.9 cc. |
| 3 | 0.1 cc. | 0.9 cc. | - | - |
| 4 | - | 0.1 cc. | 0.9 cc. | - |
| 5 | - | 0.1 cc. | - | 0.9 cc. |

0.2 cc. from each tube was then injected intracutaneously with the following result:

| | | |
|---|---|---|
| 1 | Exotoxin - antitoxin mixture. | No reaction. |
| 2 | Endotoxin - antitoxin mixture. | 35mm. x 25mm. |
| 3 | Antitoxin control. | No reaction. |
| 4 | Exotoxin control | 37mm. x 27mm. brilliant. |
| 5 | Endotoxin control | 42mm. x 28mm. |

A sixth injection was also made of 0.2 cc. of "Dick Control" (heated Dick toxin). No reaction was obtained.

Fourth week. Dick 30 x 25mm. (brilliant). Endotoxin 40 x 32 mm.

Ten /

Ten months after discharge the readings are:-

Dick 50 x 38mm. Control 30 x 20mm. Endotoxin 40 x 32mm.

The ready neutralisation of the Dick toxin in this experiment showed that the Dick reactions were due to an exotoxin and not to any other constituent. Cooke (23) has noted that toxin mixed with convalescent serum may fail to produce a reaction in some persons even although the serum contains no antibodies. It should be noted that scarlatinal antitoxin was therefore used in this patient as a neutralising agent. The skin reactions in this case spoke against a diagnosis of scarlet fever from the commencement, and their subsequent behaviour supports this conclusion. Yet the child had ample opportunity to contract scarlatina during the four weeks she spent in a Scarlet Fever ward.

When considering these apparently susceptible persons who do not develop the disease, one must not lose sight of the various non-specific factors which maintain their resistance. The patient's general resistance is dependent on many factors and there is also the local resistance of a healthy mucosa, which may apparently be lowered by trauma /

trauma etc. In 1924 Zingher (83) recorded the case of a physician at the Willard Parker Hospital who served for 3 months in the scarlet fever wards. When assigned to a diphtheria ward he developed diphtheria and this was followed by scarlet fever.

The strong reaction to the "Endotoxin" is interesting in this question of resistance, indicating according to the Japanese workers an imperfect or transitional state of immunity. Lastly, it is interesting to note that 10 months later the Dick and Endotoxin reactions are showing no material change but the "Dick Control" test is now positive for the first time.

The same neutralisation results were obtained in a definite case of scarlet fever who was showing a strong positive Dick reaction in the fifth week.

(Case 70). John G., aged 25, admitted on 1st day of illness, typical mild scarlet fever.

| | Dick. | Control. | Endotoxin. |
|---|---|---|---|
| 1st week. | 35 x 25. | 0 x 0 | 15 x 15 (faint) |
| 2nd week. | 35 x 28 | | 30 x 20 |
| 3rd week. | 40 x 30 | | 30 x 20 (bright) |
| 4th week. | 50 x 35 | | 35 x 28. |

5th week. 1. Exotoxin - antitoxin mixture 0 x 0

2.Endotoxin - antitoxin mixture 35 x 25

3.Antitoxin control No reaction

4.Exotoxin control (saline) 32 x 22

5. Endotoxin control (saline) 36 x 22

6. Dick Control (heated toxin) No reaction.

11 months later.

Dick 48 x 22. Control 0 x 0. Endotoxin 35 x 30.

The only distinguishing feature between the skin reaction in this case and the preceding one was the lack of brilliance in the Dick reaction throughout (in spite of its large size). It will also be noted that it tended to slightly increase in size from week to week, which, as I have already pointed out is not unusual in this singular type of case.

Once again antitoxin effected complete neutralisation of the Dick reaction, whereas it produced no change in the endotoxin reaction. The positive Dick reaction in this case cannot be explained therefore by the development of an allergic reaction as the Japanese workers would suggest, and its specificity is supported by the fact that 0.5 cc. of the patient's serum failed to produce any sign of blanching when injected intracutaneously into a scarlet fever rash which was easily blanched by 0.2 cc. of antitoxin /

antitoxin (1 in 10) injected as a control.

About a year has now elapsed, the patient has remained in good health and the reactions are showing no material change.

Is Dick Toxin a true toxic substance?

A large section of this study has been devoted to the description of a local erythema in the skin of certain persons following the injection of Dick filtrate in very small amounts. Further, this erythema with a few possible exceptions, appears to indicate a reliable index of the person's susceptibility to scarlet fever.

1. It has been shown that this reaction may be inhibited by the serum of scarlet fever convalescents, of artificially immunised persons, and of other Dick negative persons, due presumably to the presence of antitoxin.

2. Injections of the filtrate in large doses produce fever, malaise, vomiting and a general: :ised scarlatiniform eruption.

3. The use of convalescent serum, or, preferably, the concentrated serum of artificially immunised animals, produces marked clinical benefit on /

on these manifestations of toxaemia.

The evidence in favour of the production of a true toxin by the haemolytic streptococcus analagous to the toxin produced by the diphtheria bacillus seems therefore almost overwhelming, but it must be admitted that this "toxin" presents some rather unusual properties.

1. It shows remarkable stability for a primary toxic substance, resisting a heat of 100°C. for a considerable time. Further, it will remain potent for weeks in a diluted condition, and for years, if in concentrated form.

2. Laboratory animals manifest a high natural immunity to this "toxin", resisting large doses of the filtrate, even given intravenously, though no antitoxin can be demonstrated in their blood. This species specificity is not typical of a soluble toxin.

3. The skin of young persons is remarkably resistant, if the filtrate is to be regarded as a true toxin.

4. The Dick and Schick reactions show essential differences in their character, time of appearance /

appearance, and duration. The local effect of Dick filtrate is not so intense or so lasting as that of Schick toxin. Only the very strong positive reactions show pigmentation, which is slight, and a superficial fine scaling.

Brokman and Mayzner,(10) comparing the two reactions, pointed out that the Dick reaction was not so constant as the Schick. They found that a positive reaction frequently changed to negative:

(1) a few days after the onset of a disease.

(2) after the injection of scarlet fever toxin.

(3) after the injection of milk and various organic extracts.

They combined each toxin with adrenalin in a dilution of 1/500,000, and found that, whereas the Schick reaction became more intense, the Dick reaction was partially inhibited.

These rather curious features presented by Dick filtrate, and its apparently paradoxical behaviour in the disease itself, have caused certain investigators to conclude that "Dick toxin" is not a toxin at all, and that scarlet fever should be regarded as an allergic phenomenon, which is in no sense a toxaemia comparable to diphtheria. This conception /

conception of the disease appears to the writer to be unconvincing, but it demands further consideration.

The Allergic view of Scarlet Fever.

In 1923 Bristol (9) stressed certain points of similarity between Scarlatina, Serum Disease and Drug Hypersensitiveness and was inclined to take the view that scarlatina should be regarded as a manifestation of hypersensitiveness to the haemolytic streptococcus. He showed that in convalescence persons became skin sensitive to streptococcal proteins, but that in the acute stage this sensitive: :ness was quite absent. He believed that these active cases were in a state of desensitisation. In some instances the sensitive state would return, in others it might not.

Many other writers have from time to time advanced arguments in favour of this "allergic" view. These arguments can be reviewed conveniently by considering a series of interesting papers on the subject by Jean V. Cooke.

In the first paper (19) of the series she reported the investigation of the Dick reactions in some 200 mothers and their infants. The latter were tested in /

in the first ten days of life, and some six to twelve weeks later. She estimated skin sensitivity with 2, 20 and 50 Skin Test Doses of Dick toxin. She estimated the presence of antitoxin in the blood by the injection into Dick positive reactors of a mixture of 0.1 cc. of serum, and toxin ( 2 S.T.D. in 0.05 cc. saline), incubated previously for 1 hour. She found that the new born skin resisted large doses of scarlatinal toxin, although there might be no antitoxin demonstrable in the blood. Numbers of insensitive children had non-immune mothers with no antitoxin in their blood either, but of 53 positive mothers only 2 had positive children, and of the most sensitive group of mothers no less than 60% of children gave negative tests to as much as 50 S.T.D. of toxin. After some weeks, however, numbers of the children became sensitive to the larger doses of toxin, more especially the children with no antibody in their own blood at birth, and the children of highly sensitive mothers. In the later months of the first year of life an increasing number of children developed skin sensitivity, and in her second paper (20)
Cooke suggested that this might be evidence of a specific hypersusceptibility of the body cells to protein /

protein substances formed by scarlatinal streptococci.
(22)
She next attempted to induce this sensitivity artificially in non-sensitive persons, by giving them intramuscular injections of serum from sensitive persons, and claimed to have met with a measure of success.

(23)
In a fourth paper Cooke recorded the administration to adults and children of scarlet fever toxin intramuscularly in increasing amounts. The injections were given at short intervals and the skin tested with 2, 20 and 50 S.T.D. of Dick toxin. Within 24 hours the reaction became modified and one-third of the cases gave negative reactions in that time. During the second week some children failed to react to even 50 S.T.D. Antitoxin, however, could not be demonstrated in the blood coincidently with the loss of the skin sensitivity. Its appearance tended to be delayed and in some cases could not be found till 3 or 4 weeks had elapsed, and sometimes not at all. After a few weeks weak Dick reactions reappeared.

(24)
Lastly, typical cases of scarlet fever were investigated by similar methods. The same early decrease in skin sensitivity was noted, so that in the first week a few cases failed to react to 50 S.T.D. of /

of toxin intracutaneously. In the later weeks the loss became more marked and more constant, but in a few cases skin sensitivity returned.

Concurrently with the skin tests, samples of blood were tested for antitoxin and also for toxin, using the method described by Blake and Trask,(6) injecting 0.3 cc. of serum into the skin of Dick positive children. Toxin was demonstrable in 12 out of 13 cases from the 2nd to the 11th day of the disease, even when the rash had quite disappeared. Antitoxin, on the other hand, was not found till after the second or third week, and never till some days after the complete disappearance of the rash.

The author of these papers believes(25) that the early loss of skin sensitivity to Dick toxin resembles the phenomenon of desensitization in animals more closely than the development of skin immunity to a soluble toxin such as that of diphtheria, which requires a number of days or weeks, and suggests, that there occurs first a desensitization of the body cells and later a development of specific antibodies. She cannot accept the scarlatinal filtrate as an exotoxin, but believes that certain of the clinical features of scarlatina including the skin rash are dependent /

dependent on a bacterial anaphylactic hypersensitivity, which is presumed to be acquired from repeated infection by streptococci, and when scarlet fever occurs, the streptococcus protein is absorbed from the site of infection causing an anaphylactic response in the shape of the rash, fever, etc. The specific toxic syndrome only appears in those hypersensitive to the antigen. In others, whose hypersensitivity may be marked by specific circulating antibody there only occurs the non-specific phenomenon of pyogenic infection.

It has for long been known that mothers suffering from scarlet fever may be allowed to suckle their infants, as during the early months of life there is usually complete immunity. If the infant contracts the disease the course is almost invariably mild. Von Bormann,(7) however, has recorded as many as 18 cases, including 4 deaths, in the first year of life. The remarkable resistance of the young children's skin to Dick toxin, so clearly demonstrated by Cooke, has been confirmed by other workers.

Lichtenstein(57) in 1928 reported the results of Dick testing 100 mothers and infants.

27% /

27% of mothers and 7% of the children were positive. All the Dick negative mothers had Dick negative children, and blood from the umbilical cord blanched a scarlet fever rash. Mothers and children with positive reactions produced no blanching, and the Dick negative children from the non-immune mothers likewise showed no evidence of antitoxin in their blood. It will be seen that the factor of an inherited immunity is more clearly demonstrated in this paper than in Cooke's paper, and the relationship between the Dick test and the Schultz-Charlton reaction is very striking.

Paunz and Csoma (71) were also able to distinguish 3 groups of infants. (1) Dick positive cases with no antitoxin; (2) Dick negative cases with antitoxin; (3) Dick negative cases with no antitoxin. When the second group was injected with large doses of toxin they showed no reaction, but the third group developed sharp symptoms with, however, no eruption, indicating that the skin offered some resistance to the toxin.

To the writer it would appear that the main importance of Cooke's earlier papers lies in the fact that /

that they draw attention to the factor of local resistance as distinct from general resistance in the young child. Her later papers dealing with the disease itself stress that local immunity may develop before general immunity - in other words, that local resistance and general resistance do not always run parallel. This finding does not seem to clash necessarily with the conception of scarlet fever as a specific toxaemia, and of subsequent immunity as depending on an antitoxic factor. To assume the development of a hypersensitive state with subsequent desensitization appears to me to be hardly warranted by the evidence available.

Cooke's claim to have induced a state of hypersensitiveness in a non-susceptible person is obviously of fundamental importance, and, if substantiated, at once places the allergic conception of the disease on a firmer basis. On a closer examination of her paper, however, it appears that the persons she was attempting to sensitize were infants at an age when they might be expected to be developing Dick positive reactions naturally. Secondly, the reactions which she claimed to have produced were of feeble intensity, and usually only developed /

developed in response to large doses of toxin - 20 and 50 S.T.D. There is no mention of control tests with heated filtrate, and with such doses of toxin the specificity of the reactions obtained is therefore open to doubt. And lastly, the reactive state described did not appear for about a week. It therefore cannot be held to resemble the passive transfer of hypersensitivity in anaphylactic animals, which is usually demonstrable within 24 hours. For these reasons I consider Miss Cooke's claim to be scarcely tenable.

From time to time certain workers have maintained that the positive Dick reaction shows some correspondence to a cutaneous reaction dependent on hypersensitiveness to protein substances, and on the basis of animal experiments have been disposed to support the conception of the test as an allergic reaction. Normally, laboratory animals are insusceptible to injection of culture filtrates, but various workers have claimed to render them sensitive.

In 1925 Dochez and Sherman (34) stated that guinea pigs could be sensitized with the subcutaneous injection of streptococcal filtrate, or culture, living or dead, or the intravenous administration of dead /

dead culture. Positive skin reactions developed after 7 days and reached a peak in about one month. These apparently showed some resemblance to the Dick reaction, and they claimed that equal parts of filtrate and antitoxin incubated for 1 hour gave negative results.

In the same year Zinsser and Grinell (84) showed that streptococcal allergy could be produced in guinea pigs using agar foci, nucleoprotein extracts, Dick filtrate, or the intraperitoneal injection of living organisms. This last method was by far the most effective, being, for instance, far more potent than Dick filtrate. On the other hand, the latter was apparently the best material for the actual demonstration of such allergy by skin testing. This is an interesting finding as quantitatively it must contain much less of the body substance of the organisms than are present in the other extracts. The animals remained in a sensitive state for about six weeks.

In neither of these papers is there any mention of control tests with heated filtrate.

In 1927 Dochez and Stevens (35) carried out sensitization experiments with rabbits, using a streptococcal /

streptococcal filtrate derived from a case of erysipelas. Their paper is of added interest in that their results bear some analogy to the work about to be described in the second part of this study. The allergic reaction they described showed two distinct phases. During the earlier part of the first phase they were able to neutralise the reaction with immune serum, and the toxic principle was destroyed by heat. From about the 40th day a gradual fading of the reaction occurred, till sensitivity apparently disappeared. This was followed by a stage when all the animals gave strong reactions, which showed little specificity, in that heating or immune serum produced no diminution in the reaction.

In 1927 Mackie and McLachlan (61) corroborated the fact that it was possible to sensitize guinea pigs, so that the intradermal injection of a culture filtrate produced a cutaneous reaction. In only 5 out of 48 animals, however, was the reaction marked, and generally a high concentration of filtrate was required. They used as a control, filtrate which had been heated at 100°C. for 1½ hours, and obtained in most cases an identical result. In further tests they found that the active principle seemed to remain stable /

stable for 3½ hours. No neutralization effects were noted in sensitized animals using scarlatinal antiserum. Finally, they found that the sensitization could not be regarded as specific, for reactions were noted with similar filtrates from a non-haemolytic streptococcus, a Type I pneumococcus, and a staphylococcus. They concluded, therefore, that the cutaneous reactions were not definitely comparable with the Dick reaction in persons susceptible to scarlatina.

To the writer it would therefore appear that there is not yet sufficient experimental evidence to warrant the acceptance of an allergic basis for the Dick reaction.

## PART II.

The skin reaction in scarlet fever and in other conditions to an intracellular extract of the haemolytic streptococcus freed from all diffusible substances.

## THE OBJECTS OF THE TEST.

In discussing the anomalies of the Dick test, I have indicated that a certain proportion of individuals fail to lose their skin sensitivity to scarlet fever toxin in the course of the disease, and reach the fourth week with a skin reaction which is showing no material diminution in intensity. Some of these cases relapse, showing that in these instances the test is a reliable index of their susceptibility. I have suggested that this failure to acquire immunity is more common in the early period of childhood. It would be interesting to ascertain the serological relationship between the streptococcus causing the relapse and the one responsible for the primary infection, and also to test the skin sensitivity to filtrates from both organisms. It is possible that this apparent failure in the immunity mechanism may eventually be shown to depend on differences in the antigenic structure of different groups of scarlatinal streptococci.

The fact remains, however, that the majority of such cases do not relapse, but leave hospital in their Dick positive state. Moreover, there is considerable evidence that they remain Dick positive.

Two/

Two of the eleven cases in my series have been followed up, and a year later these two are certainly showing no loss of sensitivity. We may take it that about one person in every ten retains his Dick positive state, and yet re-infection is very uncommon. Further, it is a fact that the adult population contains somewhere between 10 and 15 per cent. of positive reactors, a percentage which is quite disproportionate to the comparative infrequency of scarlet fever in these older age groups. Some of these persons have been shown to contain antitoxin in their blood as judged by its ability to blanch a scarlet fever rash. I have already referred to the explanation advanced by Ando(1) which has found great favour with Toyoda(81) and his co-workers. These investigators ascribe a very consider-:able number of these Dick positive reactions to the development of an allergy to an "endotoxin" present in Dick filtrate. This "endotoxic" principle they consider to be, for practical purposes, identical with streptococcal nucleoprotein, and claim that they have eliminated this unsatisfactory feature of the Dick reaction by using a specially purified exotoxin in place of the standard Dick filtrate. By testing large sections of the population with this heat-labile exotoxin, freed from all impurities, and also with/

with a heat stable nucleoprotein extract, they have been able to differentiate different groups of persons in different stages of immunity. This grouping has been already briefly described. Their work throws light on the results of Kondo (53) who reported a large percentage of persons actually changing to a Dick positive state in the later stages of scarlet fever. It suggests that Kondo was using a filtrate containing a large proportion of this endotoxin or nucleoprotein principle.

When this study was started, I was anxious to ascertain whether any of the reactions reported by Kondo would be produced by a standard preparation of "Dick Toxin" widely used in this country. Dr. R.A. O'Brien kindly supplied me with a small quantity of "exotoxin" prepared in the Southern Manchurian Railway Company's Research Institute at Dairen, where Toyoda has been working. I was intending to use this purified toxin along with the ordinary commercial toxin, but the Japanese preparation had apparently deteriorated with transit and storage, for such feeble reactions were obtained, as to render it quite useless for my purpose. I therefore started using the Burroughs Wellcome toxin alone, and soon found that with this preparation the change in reaction reported by Kondo does/

does not apparently occur.

It was then that Dr. Gibson kindly offered to supply me with a haemolytic streptococcal extract freed from all diffusible exotoxin. By using this preparation along with the Dick toxin I was hopeful that I might be able to demonstrate the development of a hypersensitiveness to the extract coincident with the development of an immunity to the Dick filtrate.

There has been, however, a further impetus for pursuing this line of investigation. During the last few years numerous writers have reported cutane-:ous reactions to various streptococcal products, both in health and disease, which they believe to be due to the development of an allergic or hypersensi-:tive state. Most of this work has been focussed round the problem of rheumatic infection, and quite recently Coburn (15) in America and Collis (16) in this country have published results, which, based on a study of these skin reactions, appear to demonstrate the close association between the condition which Coburn calls the "Rheumatic State" and infection with a haemolytic streptococcus. It has appeared there-:fore that by studying the skin reactions in a series of scarlet fever cases one might obtain an answer

to/

to two questions. Can the reactions which these workers have described be regarded as in any sense specific to rheumatic infection? Can such a state of skin hypersensitiveness be shown to follow scarlet fever which is known to be caused by a haemolytic streptococcus?

## PREVIOUS WORK.

Ten years ago Bristol (9) published some results which are of interest for comparison with those obtained in the present study. He investigated the skin reactions of scarlet fever patients to "proteins prepared from cultures of specific bacteria killed, mixed, dried and ground to a fine powder". The dried streptococcus was "mostly from haemolytic strains collected from various sources including scarlet fever throats". A linear scratch was made in the skin and as much of the substance as would lie in the eye of a needle was rubbed in. A control scratch was made in the other arm.

A varying area of elevation and redness appeared, with a secondary areola of erythema, reaching its height in 24 to 48 hours, and with a raised dark red centre. In the first few days of the disease all the tests were negative. In convalescence doubtful reactions began to appear. Normal healthy controls showed a fair percentage of definite positive reactions, this percentage being higher in persons with a history of scarlet fever than in those without such a history.

In 1927 Mackenzie and Hanger (62) using filtrates/

filtrates and nucleoprotein extracts from strepto-:cocci and other pathogenic organisms, carried out intracutaneous tests on healthy individuals and patients suffering from a variety of diseases. They found that young children rarely reacted to the pre-:paration used, but that reactions tended to increase with age, so that a fair proportion of adults were "allergic" to products of one or more organisms. They were, however, unable to correlate the results of the reactions with any known previous infections in the persons tested. Further, in testing the hospital patients they could find no relation between the presence or absence of allergy and any disease or group of diseases.

In the same year Birkhaug(4) suggested that streptococcal filtrates he was using for skin testing might indicate susceptibility to rheumatism in the same way as the Dick test indicates susceptibility to scarlet fever. His suggestion was supported by Kaiser(49) who obtained somewhat similar results, but Birkhaug(5) later submitted that these filtrates were probably not true toxic substances, but rather that the persons tested were hypersensitive to them. He claimed that this hypersensitive state was present in/

in all types of acute rheumatic infection, both to non-methaemoglobin forming streptococci and green producing streptococci. The percentage of positive reactors to preparations from haemolytic streptococci was much lower.

Swift, Wilson and Todd[78] also described a high percentage of positives in rheumatics using filtrates from non-haemolytic streptococci. These filtrates were not affected by heat, and they concluded that the reactions produced were not comparable to the Dick test. When, however, "nucleoproteins" were used, the preparations from the haemolytic organisms gave larger reactions than those from non-haemolytic streptococci. (Swift, Derick and Hitchcock):[79](Derick and Fulton).[29]

Irvine-Jones[48]injected filtrates of streptococci of all types into a group of 75 rheumatic children between 5 and 15, and into a control group of 200 cripple children with no history or stigma of rheumatism. The material used was a filtrate from a 4-day culture, and was therefore a composite reagent containing not only a diffusible exotoxin but also the products of autolysis. It was found that the rheumatic group were more susceptible than the controls,/

controls, the difference being more marked when non-haemolytic filtrates were employed. In general, however, children belonging to either group who re-:sponded to one filtrate showed some response to the others. This might be explained by the supposition that such filtrates contain antigen characteristics in common. On the other hand, it might be ascribed to individual variations in the children tested. In some cases the reaction resembled a Dick reaction; it was negative when the material was heated for two hours at 100° centigrade, and in those cases the skin reaction could be neutralised. This "flat positive" type of reaction usually prevailed during the acute illness. During convalescence the re-:actions showed more induration, and lasted longer, neutralisation could not be effected, and the toxic substance was heat-stable. After the child was clinically well the reactions tended to become nega-:tive, but might again become positive. This phasic change of the skin reaction has an interesting parallel in the work of Dochez and Stevens (35) in experimentally produced allergy. The significance of skin reactions to a composite reagent of the nature used by Irvine-Jones is difficult to inter-:pret, but it is interesting to consider these findings/

findings and compare them with the results I have obtained in scarlet fever using two separate types of extract simultaneously in the same patients.

I have already mentioned the work of Coburn and Collis. Coburn[15] found that 99% of active rheumatics and 95% of patients, who had suffered from recent infection with a haemolytic streptococcus, were sensitive to the nucleoproteins of that organism. On the other hand of a miscellaneous group of 120 persons in the medical wards only 36% were positive.

Collis and his co-workers [18] in London have also been able to draw a very close relationship between rheumatic infection and skin sensitivity to streptococcal endotoxin. I have already stated that Toyoda[81] considers "endotoxin" and "nucleoprotein" for practical purposes to be identical. The American preparation of nucleoprotein is an acid precipitate of an extract prepared in a similar fashion to the material used by Collis, who also states in a more recent paper that he believes the active principles to be identical. In giving an account of my own results I shall therefore refer to the material used simply as a "Haemolytic Streptococcal Extract", and designate it for short "H.S.E."

## METHODS.

Seventy-four cases of scarlet fever were tested with extracts from haemolytic streptococci at different stages of the disease. The first 28 cases were tested at weekly intervals. The other 46 cases were tested on two occasions only - on the day of admission and again in the fourth week.

Three strains of haemolytic streptococci were used for preparing the extracts:-

(1) S.S.1., a standard laboratory culture of a haemolytic streptococcus originally isolated from a case of scarlet fever and known to produce a potent Dick toxin.

(2) N.S., a strain recently isolated from the throat of a child suffering from subacute rheumatism. This strain was chosen as being one from a non-scarlatinal source.

(3) S.2., isolated from the throat of one of the cases in the series (Case 64) as representing a recently isolated scarlatinal strain.

At first all patients were tested with S.S.1., and N.S., but as it was found that S.S.1 was giving feeble reactions, it was decided to supersede it with a recently isolated scarlatinal strain. S.2 was therefore introduced, and as it was found to give reactions exactly equal to those obtained with strain N.S./

N.S., some of the patients towards the end of the series were tested with one extract only. All the patients were Dick tested in each week of the disease in the method I have already described.

The extracts were all prepared by Dr. Gibson in the following method:-

> The 24-hour growth from 100c.cm. of phosphate broth (containing 0.2 per cent. glucose) was removed by centrifuging and washed twice in sterile normal saline. The sediment from the second washing was then transferred to a bacterio-:logical ball-mill, dried and ground. The resulting powder was then suspended in 10c.cm. of sterile saline and heated at 60° C. for 15 minutes in a water-bath. Rapid centrifuging was then employed to separate the bacterial debris. The supernatant fluid, after the addition of 0.5 per cent. phenol, was concentrated extract (H.S.E.). No chemical treatment of the organisms was applied in its preparation. The crude extract was diluted 1:100 in saline prior to skin testing.

All tests were made intracutaneously in the anterior aspect of the forearm, 0.2 c.cm. of the extract being injected. The right arm was used for the injection of the extracts (H.S.E.) and the left arm/

arm for the "Dick Toxin" and "Dick Control".

The readings were at first made after 24, 36 and 48 hours. A reaction of moderate intensity appears to be maximal at about 36 hours. At this time the weaker positives are fading, while the very strong reactions are still increasing. It was decided to record only one reading, namely the 24 hour one, and any readings which I may quote have been made at the elapse of this interval, unless otherwise stated.

The skin reactions have also been examined in 160 persons not suffering from scarlet fever. In many of these individuals weekly tests have been performed - in others only one test has been possible. They form too heterogeneous a collection to consider together in one large "non-scarlatina" group. I shall refer to them separately after I have detailed the results obtained in the scarlet fever patients.

## RESULTS: I (SCARLET FEVER).

### Age and Sex Distribution.

TABLE 9.

(showing the age and sex distribution of the 74 patients)

| Age in years | 1-5 | 6-10 | 11-15 | 16-20 | 21-30 | 31-40 |
|---|---|---|---|---|---|---|
| Males | 10 | 21 | 3 | 1 | 2 | 1 |
| Females | 9 | 16 | 3 | 3 | 5 | - |
| Totals | 19 | 37 | 6 | 4 | 7 | 1 |

### Reactions to H.S.E.

Twenty-four hours after the intracutaneous injection of H.S.E. nothing may be seen but a small area of trauma corresponding to the site of injection. This frequently takes the form of a minute papule, which may be seen for some days. This constitutes a "Negative" reaction. On the other hand, there may be a reaction varying from a feebly developed indefinite area of erythema, fading imperceptibly into the surrounding skin, to a definite positive reaction, which in its typical form presents fairly characteristic features.

In such a case there appears after some hours an area of redness, which increases in intensity to reach a maximum of perhaps 50mm. x 30mm. at the end/

end of 36 hours. In the very strong reactions this area increases still further till it may reach 80 or even 100mm. in its greatest diameter. The fully formed reaction, when typically developed, is marked off into two or more fairly clear cut zones. There is a central dark red swollen area of perhaps 20 to 30mm. in diameter, surrounded by a much paler erythema which may in turn either merge into the surrounding skin, possess a clear sharply differentiated outline, or, less commonly, a zone of pallor may surround the erythema. The dark red area is markedly oedematous and frequently right in the centre there is a paler, faintly yellowish spot or vesicle, which is almost necrotic in appearance. In these severe reactions there may be a mild degree of pain on movement of the arm, and slight tenderness is almost a constant feature of all moderate and severe reactions. Fading is rapid after 24 to 48 hours, depending upon the degree of reaction, but traces of the inner papular lesion may remain for some days. The allergic reaction thus differs from the Dick reaction, in that it tends to develop more slowly, and in the presence of the swollen and tender dark red central area.

There can be no difficulty in the recognition of the negative reaction on the one hand and the moderately/

moderately strong positive reaction on the other. In between these, however, there is every degree of reaction, and in the healthy adult a mild degree of erythema is almost the rule. Many of these reactions are of feeble character, and by the end of 24 hours are already fading. Furthermore, they merge so imperceptibly into the healthy skin that it is impossible to define the limits of the reaction with any accuracy. Their significance is open to doubt, and it is possible that by employing a higher dilution of extract, many of these feeble reactions might be eliminated. In reviewing the results, I have only accepted as a "Positive" reaction an erythema of over 20mm. in both diameters, except in one or two cases where a smaller reaction has been accompanied by swelling, tenderness and the sharp delineation, which one associates with a positive reaction. These cases have been very few in number and have occurred in small children. I realise that the fixing of the 20mm. minimum is purely arbitrary, but if one considers the character of the reaction as well as its size, this division becomes in actual practice less artificial than it would appear on paper.

I have sub-divided the positives into "Positives", "Strong Positives", and "Very Strong Positives"/

Positives" with a mean diameter of over 20mm., 30mm. and 40mm. respectively, designating them as "one plus", "two plus" and "three plus" reactions. No stronger reactions than this were encountered, because, as I have indicated, all readings have been recorded at the end of 24 hours, and at this stage the stronger reactions had not reached their full extent.

Analysis of Results.

On admission no case was showing a positive reaction and feeble reactions were singularly few. It was possible to divide them into two groups on the behaviour of the skin reaction in the subsequent weeks.

Group I. (66 cases). Out of 74 cases 66 were showing positive reactions by the fourth week, i.e., 89.2 % of the total.

Of these, 34 were Positive (20-30mm.), 25 were Strong Positive (30-40mm.) and 7 were Very Strong Positive (over 40mm.) Had further readings been taken in each case at 36 and 48 hours, larger reactions would have been recorded in many instances, but as it was not possible to do this in all the cases, only 24-hour readings have been considered for the sake of uniformity.

Group II /

Group II. (8 cases). Only 8 cases (10.8%) failed to develop definite positive reactions. The oldest of these patients was aged 7 years. 5 such cases were exhibiting on admission the type of poorly defined erythema of between 15 and 20mm. in diameter, which I have described, and week after week this showed no material change either in size or in character. The other 3 cases were children aged 1, 2 and 3 years respectively, who, while they appeared to be "dead negative" on admission, had developed by the fourth week an erythema of 10mm. in mean diameter. It is doubtful whether these children would ever have developed into "positive" reactors. One of them remained Dick positive and relapsed in the fifth week. (Case 11.)

Effect /

Effect of Age on the Reaction.

The effect of age on the reaction can be seen from the following Table:-

TABLE 10.

| Age Group | Cases in Group | Negatives | + Reactions | ++ Reactions | +++ Reactions |
|---|---|---|---|---|---|
| 1- 5 | 19 | 6 | 9 | 3 | 1 |
| 6-10 | 37 | 2 | 21 | 13 | 1 |
| 11-40 | 18 | 0 | 4 | 9 | 5 |
| Totals | 74 | 8 | 34 | 25 | 7 |

Comment. All the cases over 7 years of age became positive, and from a study of the 28 cases which were tested every week, it was noticeable that the allergic reactions tended to appear earlier in the older age groups.

Relation between H.S.E. and Dick Reactions.

Prior to testing the series of cases above, a small number of preliminary tests were made with H.S.E. on scarlatina convalescents, who had been tested throughout their illness with Dick toxin. The results obtained showed some features of interest, and are detailed in the following Table. The readings recorded are the mean diameters in each case. The sixth patient was included for interest, though the diagnosis was in doubt.

TABLE 11.

| Case Number | 1st Week Dick | 2nd Week Dick | 3rd Week Dick | 4th Week | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Dick | 24hrs. S.S.1 | 48hrs. S.S.1 | 24hrs. N.S. | 48hrs. N.S. |
| 158 | ?0 | 15 | 10 | 14 | 17 | 10? | 30 | 42 |
| 159 | ?0 | 15 | 15 | 10⊗ | 15 | 10? | 31 | 45 |
| 115 | 19 | 10 | 0 | 0 | 21 | 10? | 30 | 35 |
| 110 | 25 | 0 | 0 | 0 | ※21 | 10? | 27 | 32※ |
| 118 | 28 | 28 | 22 | 24 | 10 | 0 | 19 | 10 |
| Barbara H. (non-scarlet.) | 28B | 39B | 38B | 34B | 10 | 0 | 16 | 0 |

※ The H.S.E. readings for Case 110 were made in the third week.
⊗ The Dick reaction became negative in the fifth week.

Comment. Five cases of scarlatina tested in convalescence gave positive reactions to H.S.E. 4 of these were strongly positive; the 5th case gave a weaker reaction and this was associated with a strong positive Dick reaction.

A 6th case, where the diagnosis of scarlet fever was in doubt, retained a brilliant Dick reaction and was negative to H.S.E.

These two last cases suggested a definite relationship between sensitivity to Dick toxin and to H.S.E.

The tendency for the stronger H.S.E. reactions to increase beyond 24 hrs. while the weaker readings fade is clearly shown; also the marked difference between S.S.1 and N.S.

In the following Table are the results of another small series of preliminary tests amongst the medical staff. All the persons tested were in the 25 to 30 age group, and all had had scarlet fever in childhood.

TABLE 12.

| Name | Dick | | S.S.1. | | N.S. | |
|---|---|---|---|---|---|---|
| | Toxin | Control | 24hrs. | 48hrs. | 24hrs. | 48hrs. |
| J.L.H. | 0 | 0 | 32 | 30 | 58 | 80 |
| H.R. | 0 | 0 | 37 | 32 | 52 | 52 |
| R.A.P.M. | 25 | 0 | 17 | 16 | 37 | 33 |
| J.M.F. | 0 | 0 | 0 | 0 | 18 faint | 10 |
| J.P.M. | 0 | 0 | 0 | 0 | 10 | 0 |

Comment. The relationship here is not so clear. There were here two very strong reactors and two negative reactors with an intermediate reactor of moderate strength who was also Dick positive.

In the following Table the whole series of 74 Cases are grouped according to the coincident changes in the Dick reaction, judged by weekly testing.

TABLE 13.

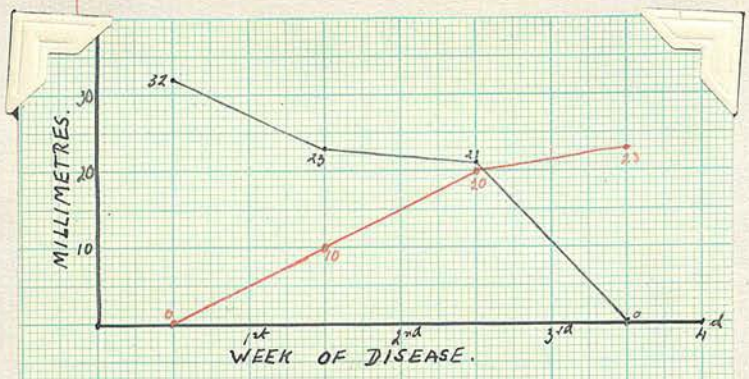
| Group | H.S.E. On admission | H.S.E. On discharge | Dick test. On admission | Dick test. On discharge | Cases. |
|---|---|---|---|---|---|
| I | - | + | + | - | 53 |
| II | - | + | - | - | 11 |
| III | - | + | + | + | 2 |
| Cases developing allergic reaction | | | | | 66 |
| IV | - | - | + | - | 7 |
| V | - | - | - | - | 0 |
| VI | - | - | + | + | 1 |
| Cases not developing allergic reaction | | | | | 8 |

Comment. 60 Cases showed the usual change in the Dick reaction from positive to negative, but 7 of them failed to develop a positive reaction to H.S.E.

On the other hand, of the 3 cases which remained Dick positive, 2 became sensitive to H.S.E.

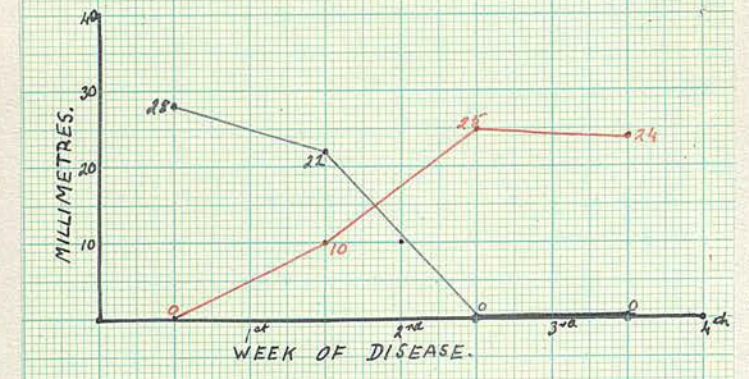
It does not seem possible on the basis of these results to distinguish any close relationship between the two reactions.

It /



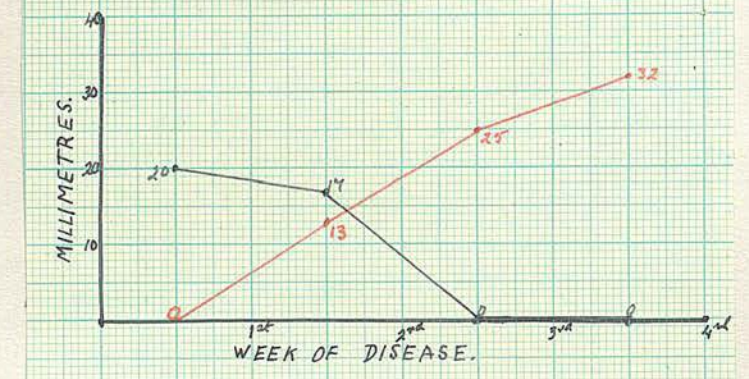

Case 83.

Lottie S., aged 7.



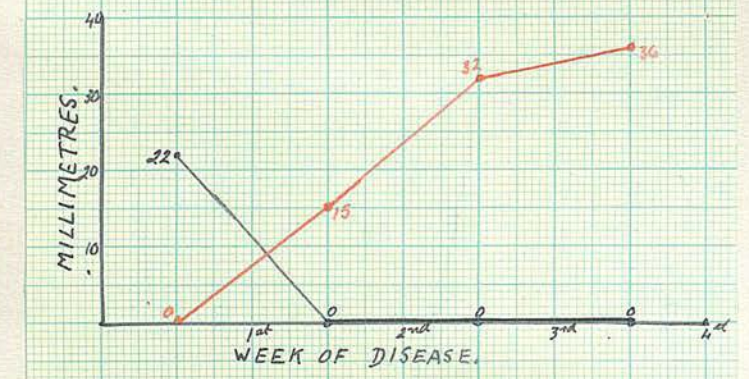

Case 79.

Charles W., aged 5.



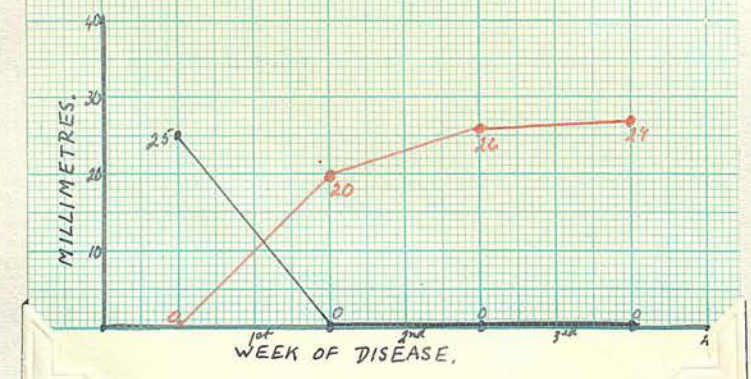

Case 77.

John C., aged 13.




Case 72.

Ina McE., aged 13.




Case 68.

Anne R., aged 6.

It is obvious that a person may be sensitive to Dick toxin and to H.S.E. at the same time. In the great proportion of the cases, however, the patients on admission were Dick positive and H.S.E. negative, while on discharge they were Dick negative and H.S.E. positive. It was instructive to study the changes in these patients from week to week. Some examples will be found on the opposite page.

They suggest, further, that where the Dick positive state tends to persist till late in convalescence, the allergic reaction tends to be slow in appearing; on the other hand, when the characteristic change in the Dick reaction has occurred by the time of the second test (as in the fifth example), the allergic reaction appears more rapidly.

There may, however, be no specific relationship between the two reactions, the explanation resting rather in the ages of the subjects tested. I have already shown that in the younger children, there is a less constant development of sensitiveness to H.S.E.; I have also suggested, in the earlier part of this study, that there is a "lag" in the development of immunity as judged by the appearance of a Dick negative state on weekly testing.

Results /

Results with different Strains.

One has already referred to the difference in the degree of reaction obtained with the strains of haemolytic streptococci "S.S.1." and "N.S.". This difference can be clearly noted in Table 12 and Table 13.

S.S.1 was a scarlatinal strain which had been maintained in culture for many years. A fresh strain "S.2. was therefore obtained from the throat of Case 64, and an extract prepared in the method described. When tested in parallel with the extract N.S., the following are the reactions which were obtained in five consecutive convalescent cases.

TABLE 14.

| Reagent used in skin test. | Actual Readings in Millimeters. | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Extract S.2. | 35x24 | 30x20 | 35x28 | 45x35 | 33x22 |
| " N.S. | 38x24 | 30x20 | 34x28 | 42x30 | 32x22 |

These two extracts prepared from two different strains of haemolytic streptococci, the one from a case of scarlet fever and the other from a case of subacute rheumatism, were apparently identical in their content of skin reacting principle.

In/

In order to ascertain whether any serological relationship existed between strains S.2 and N.S., Dr. Gibson kindly carried out direct agglutination and agglutinin absorption tests with antiserum to strain N.S., which was available. His report was as follows:-

> "The antiserum to strain N.S. gave strong agglutination of the homologous strain in dilution 1:3200, but did not agglutinate strain S.2 even in dilutions 1:50. S.2 did not absorb any effect for strain N.S., the end titre after absorption being still 1:3200. It could thus be said that the strains were serologically unrelated."

The point is of interest in any attempt to decide on the precise nature of the skin-reacting substance in the haemolytic streptococcus.

## RESULTS: II (NON-SCARLATINA)

In the following pages will be found the results of testing 160 persons not suffering from scarlet fever with haemolytic streptococcal extract.

### Results in Health.

The results have already been described of the cutaneous reactions to H.S.E. of five members of the medical staff of the Edinburgh City Hospital. There were two very strong reactors; one was moder-:ately strong and two were negative. Four of these subjects were being exposed every day to haemolytic streptococci in fairly concentrated doses, and they cannot be regarded as normal individuals from that point of view.

Twenty-eight medical students were tested with H.S.E. (S.2.). All were apparently in good health, and none were in contact with scarlet fever cases.

Accepting 20mm. as a minimum positive re-:action there were six positive reactors. One of these gave a strong positive (3 plus) reaction. He had not had scarlet fever, but had been immunised 13 months previously because of a brilliant Dick reaction which was now negative. The other five gave one plus/

plus reactions, - two of them had had tonsillitis followed by tonsillectomy; one gave a history of scarlet fever 13 years previously: the other two gave no history of any previous streptococcal infection.

There were 22 negative reactors; but of these, nine gave a feeble erythema between 10 and 20 mm. in size with an indefinite outline which made accurate measurement extremely difficult. Of the 22 subjects, eight gave a history of scarlet fever in childhood.

Relation of reactions to previous infections.

It was therefore not possible to define any association between the skin reactions to H.S.E. and any previous infection.

Retests.

Eighteen of the persons tested were retested in 4 weeks' time. In two instances the reaction had slightly increased; in five instances it had slightly decreased; in no case was there any material change.

Relation to Dick test.

In sixteen cases the Dick reaction was also investigated. Five gave positive reactions. No definite relationship was found to exist between the reactions to Dick toxin and to H.S.E.

## RESULTS: II (NON-SCARLATINA).

### Results in Diphtheria.

12 patients suffering from diphtheria were also tested with H.S.E. The results can be seen in the following Table, where the patients have been arranged in order of age.

TABLE 15.

| Name. | Age. | Units D.A.T | Tested on - | Result. |
|---|---|---|---|---|
| Peter F. | 3 | 20,000 | 3rd day | - |
| James S. | 4 | 32,000 | 6th " | - |
| Chris S. | 4 | 24,000 | 9th " | - |
| Mary G. | 7 | 16,000 | 12th " | - |
| Mary M. | 8 | 30,000 | 11th " | - |
| Bill M. | 8 | 8,000 | 9th " | - |
| Norman M. | 8 | 10,000 | 2nd " | - |
| Eliz. M. | 9 | 150,000 | 70th " | - |
| John C. | 10 | 24,000 | 12th " | - |
| Alex. L. | 15 | 50,000 | 16th " | + |
| Ann S. | 16 | 13,000 | 5th " | + |
| Effie T. | 16 | 6,000 | 2nd " | +++ |

Comment. The results emphasise the importance of the age of the patient tested. Five of the negative patients were re-tested four weeks later. All were still negative.

## Results in Measles.

30 children suffering from measles were tested with H.S.E.

Their ages varied from one to ten years, but 22 of them were under five years. 20 of them were convalescent cases in the third or fourth week from the onset of the infection.

Results. All were negative. The oldest child in the ward tested on the twentieth day of the illness gave a border line reaction measuring some 20 x12mm, but difficult to define and too indefinite to be regarded as a positive reaction. She gave no history of previous scarlet fever, but her Dick reaction was negative.

The results contrast sharply with those obtained in convalescent scarlet fever patients, and once again suggest the importance of the age factor.

Puerperal Infection.

21 cases have up till the present been tested with H.S.E. intracutaneously. Most of these patients have been retested at weekly intervals. The number of tests made in each case has varied consider-:ably, and in some cases testing has only been started in convalescence. I therefore do not propose to describe the results obtained in detail.

In 14 cases the reaction has been negative at the first test, while 7 have given positive (one plus) reactions.

In 14 cases it has been possible to carry out three, four or more tests in the succeeding weeks, and in 5 of these cases there has been a notable increase in the intensity of the reaction; 6 cases have remained negative and 3 have remained positive without showing any material change.

All the patients who have been seriously ill have given negative or feeble reactions. It has therefore not been possible to ascribe with certainty any subsequent increase in reaction to the specific effect of infection with a haemolytic streptococcus.

## Results in Erysipelas.

The skin reactions to H.S.E. in erysipelas, another streptococcal infection, are of considerable interest. 30 patients have been investigated, and the results are detailed in Table 16.

TABLE 16.

| | Name | Age | Day of Test | Reaction in millimeters | Remarks. |
|---|---|---|---|---|---|
| 1. | Louis O. | 16 | 4th | 50 x 25 | Active |
| 2. | Geo. N. | 54 | 20th | 30 x 27 | Active "wandering" type |
| 3. | Olive E. | 40 | 7th | 35 x 22 | Subsided. |
| 4. | Mrs. W. | 47 | 24th | 40 x 27 | Subsided. |
| 5. | Mrs. F. | 56 | 7th | 27 x 27 | Active. |
| 6. | Mrs. P. | 50 | 11th | 30 x 30 | Subsided. |
| 7. | Mrs. R. | 55 | 2nd | 70 x 45 | Active. |
| 8. | John P. | 51 | 3rd | 30 x 25 | Active. |
| 9. | William B. | 66 | 3rd | 23 x 22 | Active. |
| 10. | Susan S. | 20 | 11th | 35 x 18 | Subsided. |
| 11. | Helen H. | 39 | 3rd | 10 x 10 | Severe burning. Died. |
| 12. | Mrs. McD. | 44 | 2nd | 30 x 28 | Active. |
| 13. | Mrs. C. | 54 | 7th | 34 x 22 | Subsided. |
| 14. | Mrs. B. | 46 | 8th | 32 x 22 | Subsided. |
| 15. | Mrs. C. | 60 | 16th | 35 x 25 | Active "wandering" type. |
| 16. | Sam D. | 42 | 7th | 28 x 18 | Active. |
| 17. | Margt.C. | 8 | 6th | 27 x 18 | Active. |
| 18. | Adam M. | 55 | 5th | 0 x 0 | Not erysipelas. Removed to R.I.E. with subacute mastoiditis and sub-:periosteal abscess. |
| 19. | Mrs. H. | 75 | 12th | 30 x 25 | Active. |
| 20. | Mrs. B. | 71 | 18th | 30 x 24 | Subsided; febrile due to abscess. |
| 21. | Harriet P. | 20 | 5th | 20 x 16 | Active. |
| 22. | Mrs. McL. | 48 | 8th | 35 x 25 | Active. |
| 23. | Louisa M. | 28 | 8th | 35 x 20 | Subsided. |
| 24. | Mrs. D. | 54 | 14th | 30 x 20 | Subsided. |
| 25. | Mrs. F. | 40 | 9th | 22 x 20 | Active. |
| 26. | Isa R. | 63 | 4th | 18 x 15 | Gravely ill. |
| 27. | Mrs. S. | 40 | 7th | 24 x 18 | Subsided. |
| 28. | Archie W. | 31 | 9th | 20 x 17 | Acutely ill. |
| 29. | Wm. K. | 65 | 7th | 15 x 12 | Acutely ill. |
| 30. | Gerald C. | 2 | 3rd | 0 x 0 | Acutely ill. |

Comment /

Comment. Excluding the case wrongly diagnosed, 27 out of 29 cases of erysipelas gave positive reactions.

Of the two negative reactors, the one was a case of severe burning almost moribund when tested; the other was a child of 2½ years, acutely ill.

The only other child in the series gave a positive reaction.

In many cases reactions of considerable intensity were obtained, even in the presence of a sharp pyrexia, e.g. Cases 1 and 7. These reactions to H.S.E., however, did not resemble the reactions which I have previously described. In erysipelas the central dark red area with surrounding erythema is seldom seen. The reaction produced takes the form of a uniform pink or red erythema, with a slightly raised sharp margin clearly differentiated from the surrounding skin, not altogether dissimilar from the erysipelatous lesion itself. Tenderness, however, is very slight; the patient does not complain of pain or burning, and the most severe reactions encountered showed no tendency to bleb formation.

Cases 26, 28 and 29 have been accepted as positives though the mean diameter did not reach 20mm. The character of these reactions left no doubt as to their true nature; they were in fact miniature reactions in patients who were gravely ill.

## Medical Cases.

34 patients in a general medical ward were tested intracutaneously with H.S.E.

The age of the patients varied from 9 to 65 years.

13 patients (38%) gave positive reactions. The results are shown in the following Table.

TABLE 17.

| Diagnosis. | No. of Cases. | Reaction. |
|---|---|---|
| Rheumatic Infection (febrile) | 2 | + |
| Rheumatic Infection (afebrile) | 1 | ++ or +++ |
| Chorea | 2 | + |
| Rheumatoid Arthritis | 2 | ++ or +++ |
| Bronchitis & Asthma | 2 | + |
| Chronic Nephritis | 1 | ++ or +++ |
| Haematuria (cause ?) | 1 | + |
| Secondary Anaemia | 1 | + |
| Cases positive to H.S.E. | 13 | |
| Gastric Cases | 5 | all negative |
| Respiratory Cases | 5 | all negative |
| Tuberculosis | 4 | all negative |
| Cardiac Cases (old rheumatic) | 5 | all negative |
| Apoplexy | 1 | negative |
| Goitre | 1 | negative |
| Cases negative to H.S.E. | 21 | |

Retests /

Retests.

10 cases were tested at weekly intervals for a month or more. None showed any material change except the 4 strong positive reactors. These showed a minor degree of fluctuation from week to week, e.g. Jean S., aged 15. Rheumatic fever followed by mitral incompetence.

Testing was started in the 12th week of disease, and the reactions were as follows:-

| | |
|---|---|
| 12th week | 37mm. x 27mm. |
| 13th week | 36mm. x 25mm. |
| 14th week | 45mm. x 35mm. |
| 15th week | 45mm. x 38mm. |
| 16th week | 40mm. x 30mm. |

## DISCUSSION.

It would appear from these results that in a proportion of cases, infection with the haemolytic streptococcus may produce a condition of hypersensitive-:ness to intracellular products of this organism. This finding brings streptococcal disease into line with a number of infections known to result in allergy to the specific antigen.

### Nature of Skin Reacting Principle.

The exact nature of the active principle responsible for the skin reactions which I have described, is still uncertain. Nor is it known whether it is present in all groups of haemolytic streptococci. In the present study only three strains have been used, and it is not possible to draw any conclusions therefrom. As, however, identical results were obtained from two strains serologically unrelated, it seems possible that all haemolytic streptococci may eventually be shown to share the same skin reacting principle. It seems also likely that the potency of this active principle may deteriorate after prolonged laboratory culture. As to whether this principle is shared by all streptococci, Lancefield (54) in 1925 demonstrated a nucleoprotein fraction/

fraction common to all types. Collis[18] and his co-workers state that extracts made from green producing streptococci and also from the "gamma" type of Birkhaug have produced much weaker reactions, and that it has not been possible to correlate the reactions obtained, each extract being apparently specific with no common active principle.

The extract used in this study, whatever its active principle may eventually prove to be, cannot be regarded as a general poisonous substance, as it has only produced reactions in sensitive persons. Even if we accept the specificity of the substance used, there remains the possibility that the sensitiveness of the person tested was not specific. It is true that a positive reaction might be regarded merely as the expression of a general sensitivity. Collis, however, reports that he has tested some 30 persons, whose reactions to H.S.E. were known, with extracts made from B.Coli and Pneumococci and also with Tuberculin and Schick toxin. He has been unable to find any correlation between the reactions produced, and is convinced that the skin reaction to H.S.E. must be regarded as specific.

The/

The Results of Bristol.

The results which I have obtained show a striking resemblance to those obtained by Bristol (9) ten years ago, using a dry preparation of streptococcus protein by the percutaneous route. Believing that scarlet fever was an anaphylactic phenomenon, Bristol ascribed the negative reactions which he obtained during the illness to these patients being in a state of desensitisation. This might apparently be only a temporary state, as the reactions tended to reappear later, and were present in a considerable proportion of normal persons with a previous history of scarlet fever.

Bristol showed that normal persons without such a history were also skin sensitive to the product he was using, and I have shown that normal persons, who have not previously suffered from a recognisable streptococcal infection, may give positive reactions to the intracutaneous injection of H.S.E.

Non-specific Inhibition of Reactions.

It might be argued that the reactions, which have been so prominent a feature in the scarlet fever convalescents I have tested, have not arisen de novo.

On first consideration it seems possible that/

that a pre-existing allergic state may have been suppressed during the febrile stage of the illness, and have reappeared in convalescence. Of the 56 patients in the age-period 1 - 10 years, no fewer than 48 developed positive reactions (86%). Coburn in New York, Collis in London and Gibson and Stewart in Edinburgh, are all agreed, however, that such reactions occur only in a minority of urban children. Any suggestion that the children in my series of cases were all skin positive before their illness began, is quite untenable.

There is, nevertheless, strong evidence that allergic reaction may disappear during periods of fever or extreme weakness from any cause. Mackenzie and Hanger (62) in using their preparations found that a positive reaction might be obtained in a patient during convalescence, who failed to react during the febrile phase. I have shown that in severe cases of puerperal infection the skin reaction to H.S.E. is negative, and that in exceptionally severe cases of erysipelas, it appears to be partially inhibited. Positive reactions in adult life are more common than in childhood. In my cases, however, every person over 7 years of age developed a positive reaction, and one cannot assume that all these patients were/

were merely showing the recrudescence of a temporarily suppressed reactive state. No case in my series could be regarded as seriously ill. Even cases with sharp pyrexia were excluded, owing to the routine administration of anti-toxin. Thus only mild cases were investigated, and it does not seem to me feasible that the degree of systemic disturbance present in any case could have inhibited the reaction. Fever, of itself, does certainly not have this effect. The most severe reaction I have yet seen in scarlet fever, occurred in a case of scarlatinal arthritis with a temperature of 101.6° F. and positives have frequently been noted in the erysipelas cases with a temperature higher than this. I am convinced that if loss of skin reactivity has been a factor in producing the results I have obtained in this series of cases, this has been the result of local changes in the capillary circulation due to the presence of the exanthem. In spite of the work of Lewis and other investigators, our knowledge of the reaction of the skin in health is still very imperfect, and the reaction in disease is still more obscure. As, however, it is not possible to apply this explanation to the younger patients, who, incidentally, have formed the bulk of my cases, there seems to be no good reason for applying it to the/

the adult patients. The evidence therefore all seems to suggest that the allergic condition as shown by the cutaneous reaction during convalescence, was the result of the infection, and had not existed in the patients before the disease commenced.

Control Patients.

It seemed to me that another possible fallacy was that the weekly repetition of the test might be contributing in some way towards the development of a positive reaction. It seemed hardly likely that one could be producing a specific sensitisation of the subjects tested, but Mackenzie and Hanger (62) reported that repetition of injections on the same area of skin seemed to produce some non-specific acceleration of their reactions.

In order to be able to completely exclude any such fallacies, I decided after testing the first 28 patients, to perform only one re-test; to select a different area of skin for re-testing; to study the effect of weekly tests on a series of control cases, preferably adults, as I had already learned that adults appear to develop these allergic reactions more readily than do children.

The second series of scarlatina cases, tested/

tested twice only, have produced an even higher percentage of allergic reactions than the first. Further, a wide variety of subjects retested every week have shown no material change in their reaction. Only minor variations occur, and these may be in either direction.

Comparison of Results with previous Work.

I have already referred to the results obtained by Irvine-Jones (48) in rheumatic children, where a "flat positive" type of reaction usually prevails during the acute illness, but during convalescence the reactions showed more induration and lasted longer, neutralisation could not be effected and the toxic substance was heat stable. I have pointed out that this worker was using a composite reagent containing both extracellular and intracellular material. Her results showed an interesting analogy to those of Dochez and Stevens (35) whose work I have already referred to in a consideration of the nature of the Dick test. These workers in attempting to induce a Dick positive state in rabbits reported that they were able to demonstrate two distinct phases of sensitisation. In the early stages, filtrates of haemolytic streptococci produced a "flat" type of erythematous/

erythematous reaction, and their effect could be neutralised with specific antiserum. When heated filtrate was used no reaction occurred at this stage. Later, the reaction was papular in type, no neutralis-:ation with any serum was possible, and the reacting substance in the filtrate was now thermostable. In scarlet fever the Dick reaction has been thought to correspond with the first phase.

The present work shows that while both a Dick positive phase and an allergic phase may occur together, they are typically found at different times in the course of the illness. It also shows that the reagents necessary to elicit the two types of reaction are essentially different. The early flat erythema is produced by the diffusible products of the organism as found in filtrates of young fluid cultures, while the later papular type of lesion is a response to material from the bacterial bodies freed from extracellular toxins.

Relationship between Reactions to H.S.E. and Dick Toxin.

I have shown that in scarlet fever, the skin sensitivity to Dick toxin and to H.S.E. seem to be in many cases inversely related, but on studying the reactions from week to week over the whole series of cases/

cases, it can be seen that the relationship is not a constant one.

In erysipelas the skin appears to be almost constantly sensitive to H.S.E. and insensitive to Dick toxin.

On the other hand, in testing normal persons with both reagents, I have been unable to correlate the two reactions. This is in keeping with the find-:ing of Collis (16) in rheumatic cases, who has stated that a positive reaction to H.S.E. gives no indication of what the Dick reaction may be.

Mechanism of these Allergic Reactions.

The mechanism of these allergic skin reactions has been studied at length by Zinsser (84,85) and his co-workers. They have shown that this "allergy of infection" is essentially different from the development of an anaphylactic state. The latter may be induced by the injection of bacterial proteins, as with almost any other protein, is associated with the development of circulating antibodies and is passively transferable to another animal. It is not comparable with the allergy which results from infection with the same organism. These workers have contrasted the hypersensitiveness following injection with/

with that resulting from infection.

This allergy of infection or altered reactivity of the body cells, appears to be part of the normal defensive mechanism and may be a stage in the production of immunity. The interpretation of these reactions as regards immunity to scarlet fever has been already considered in discussing the results obtained by Toyoda [81,82] and his colleagues.

Scarlatinal Nephritis.

The clinical significance of the development of this highly allergic state in the later stages of scarlet fever is still difficult to assess, but is of considerable interest in the consideration of its possible relationship to two complications, nephritis and arthritis.

It has for long been realised that acute nephritis is often a sequel to some infectious process. This infection is not uncommonly situated in the throat and is frequently due to a haemolytic streptococcus. As to the relative importance of this infective factor in the causation of nephritis there is still no agreement, and the actual mechanism by which it may produce these later kidney changes is still obscure.

In scarlet fever toxic changes in the kidney are/

are sometimes met with in the acute stage of the illness, but true nephritis is usually a late complic-:ation developing about the beginning of the fourth week. The later changes which occur do not appear to be due to a local infection, nor can they be shown to be directly due to the action of a diffusible toxin. It is held by some clinicians that the administration of scarlet fever antitoxin lowers the incidence of nephritis, but statistical proof of this is difficult to obtain. Its value in the prevention of this complication is certainly by no means established. Attempts to produce experimental nephritis in animals with organisms or toxins have been generally disappointing, though partial successes have been claimed.

It has been suggested that the onset of an attack of acute nephritis is dependent not exclusively on the acute infection, but, in addition, upon an altered reaction of the body to the infection - an allergic state, which might render the cells and capillaries of the kidney peculiarly vulnerable to injury. The persistence of the infection in the throat or elsewhere may result in the liberation of some bacterial product into the circulation, and in this way give rise to renal damage in the later stage of/

of the illness.

Lukens and Longcope (59) without success attempted to produce a chronic infection in the paranasal sinuses of goats using haemolytic streptococci, with the idea of reproducing conditions, which would be analagous to those in man. When they injected not Dick toxin but suspensions of killed haemolytic streptococci into the left renal artery, they produced a glomerulitis in a proportion of cases. They found, however, that the incidence of this glomerulitis could be greatly increased, if they first established an acute local streptococcal infection by the intra-:cutaneous injection of living haemolytic streptococci. This local infection was followed in 5 - 10 days time by a condition of hypersensitiveness, which they estimated by the appearance of an erythematous skin reaction to the intradermal injection of "filtrates of haemolytic streptococci".

In the series of 74 cases of scarlet fever which I have described, no patient has developed nephritis. The incidence of nephritis in the Edinburgh City Hospital is now only about 2%, and several months may pass without a case occurring. In the few cases of nephritis which I have had an opportunity of skin testing, there has been no finding of interest.

The/

The patients as judged by their skin reactions were in an "allergic state", but so also were the uncomplicated cases. It would appear from these few cases, therefore, that if the development of an allergic state is indeed a factor, it can not be the only factor.

Scarlatinal Arthritis.

In scarlet fever arthritis tends to be an earlier complication than nephritis, and may occur as early as the first week of the disease. The beginning of the second week is probably the most usual time for the onset of symptoms. It is at about this period of the illness that an allergic state, as judged by a positive skin reaction to H.S.E., usually develops. This is more particularly true of the adolescent patient, who, incidentally, is known to be especially liable to this complication.

In the series tested, there were a few instances of an early joint complication, but this took the form of a mild arthralgia rather than a definite arthritis. In these cases the skin reactions on the first retest was positive, but too much importance must not be attached to this, as this early sensitivity would appear to be general in patients of this age.

I have had an opportunity of testing one fairly severe/

severe scarlatinal arthritis, not included in the above series. This was a boy of 16 years, in the fourth week of the disease. At the time of testing there was a fair degree of pyrexia (101 to 102° F.) and considerable constitutional upset. The usual intracutaneous injection of H.S.E. produced a reaction of 75 x 35 mm. at the end of 24 hours. This is the largest reaction I have seen in a scarlet fever patient.

H.J. Gibson and W.A.R. Thomson (results unpublished) have obtained a relatively low percentage of positive reactions in the acute febrile cases. They are inclined to attribute this to a non-specific inhibition of the skin reaction due to the associated systemic disturbance. The intensity of the reaction in the above case does not support this view, and I have formed the opinion from my results in erysipelas and other acute infections, that constitutional disturbance has to be extreme before the skin reaction to H.S.E. is materially affected. On the other hand, in chronic carditis, tuberculosis and wasting conditions generally, negative reactions would appear to be frequent. This is also the finding of Collis, Sheldon and Hill.(18) While not wishing to draw undue inferences from this one case, when considered in/

in the light of Gibson and Thomson's findings, it would appear to have some definite bearing on the ethiology of acute rheumatism.

There appears to be an essential difference between the reaction of the skin to H.S.E. in scarlatinal arthritis and in acute rheumatism. Does this not suggest that the causes of these two conditions may be essentially different? Scarlatinal arthritis occurs in the course of a known streptococcal infection, and the skin reaction to H.S.E. is positive. The occurrence of a negative reaction in acute rheuma-:tism would indicate that the importance of the haemolytic streptococcus in this condition has been over-estimated. This is in accord with the general conclusion of Gibson and Thomson and does not support the recent findings of Collis (18) and his co-workers.

Relationship of Scarlet Fever to Acute Rheumatism.

The persistence of this allergic state is of interest and requires further investigation. The etiological importance of scarlet fever in the subsequent development of acute rheumatism has been disputed. If we are willing to regard acute rheumatism as being based on a condition of allergy to the haemolytic streptococcus, the importance of the present/

present study is obvious, in that I have been able to show that this allergic condition develops in the course of scarlet fever. On the other hand, the specific causal relationship of the haemolytic streptococcus to rheumatism is still "non-proven", and Gibson and Thomson, in what is admittedly a small number of cases, have been quite unable to substantiate the etiological importance of scarlet fever in acute rheumatism.

I have been able to retest 3 cases with H.S.E. about a year after their scarlet fever. The reaction in each case appears to show no material change from the last reading obtained in hospital. Two of the cases I have already described in detail pp. 85, 88. The third case has come by chance under my notice again, owing to his being admitted to the Royal Infirmary, suffering from chorea. (Case No. 92).

Influence of Age in Reaction to H.S.E.

From all the cases studied, both in the scarlatina and the non-scarlatina groups, the import-:ance of the age factor has been evident. Collis[18] has shown that increase of sensitivity to H.S.E. with age seems to run parallel with the increase of sensitivity to tuberculin (as recorded by Hart[44]) only up/

up to age 14. After that, the number of positive reactors to H.S.E. does not continue to increase as does the number of reactors to tuberculin. Similar findings have been recorded by Derick and Fulton (29) and Gibson, Thomson and Stewart.(38)

Medical Cases.

The actual results obtained in the medical group of patients do not merit any lengthy discussion. Their importance lies in the fact that they show that repeated testing in the absence of streptococcal infection produces no change in the skin reaction to H.S.E.

Apart from the case of chorea referred to above, the other cases of rheumatic infection were also skin sensitive to H.S.E., but no conclusions can be drawn from the results in so few cases.

The markedly strong reaction in the case of erythema nodosum is of some interest. The tissue hypersensitivity to minute quantities of H.S.E. in this condition has already been described by Collis.(17)

## SUMMARY AND CONCLUSIONS.

(Part I ).

1. The test of susceptibility to scarlet fever first introduced by the Dicks has been described. Its relationship to the Schultz-Charlton phenomenon and to the etiology of scarlet fever has been considered.
2. The divergent results obtained by other workers have been briefly presented.
3. 160 cases of scarlet fever have been skin tested at weekly intervals. The methods adopted and the results obtained have been described and summarised.
4. The anomalies of the test as noted in these cases and as described by other workers have been reviewed.
5. An attempt has been made to assess the relative importance of these anomalies.
6. The conception of scarlet fever as an allergic phenomenon has been considered.

From a survey of this work it seems possible to form the following conclusions:-

1. That in general the Dick test forms a reliable index of susceptibility to scarlet fever is in /

in my opinion unquestionable.

2. The paradoxical behaviour of the test has been to some extent exaggerated. It is possible that some of the anomalous features described may be due to the development of an allergic state.

3. Scarlet fever is due to infection with a haemolytic streptococcus. It is not a disease entity, but is a clinical syndrome, of which an eruption of particular character and distribution forms an essential feature. The continued use of such an expression as "Scarlatina sine Eruptione" can only lead to confusion. In any consideration of the value of the Dick test some such definition as the above must be accepted by all workers, if comparable results are to be obtained.

4. If scarlet fever is to follow such an infection, three conditions are necessary:-

(1) The infecting streptococcus must be highly toxigenic.

(2) The host must have an insufficient general immunity.

(3) The skin of the infected person must be susceptible to the toxin.

General and local resistance are not necessarily parallel. /

parallel.

5. The fact that in certain persons and at certain periods of life they do not run parallel does not form a sufficient reason for the discarding of the view that scarlet fever is caused by a specific toxin.

6. The conception of scarlet fever as an allergic phenomenon is based on a series of inconclusive animal experiments, a fallacious assump: :tion that general and local resistance must coincide, and a too destructive criticism of the Dick test.

7. The conception of scarlet fever as a specific toxaemia is more convincing. From the available evidence it is at present the only one acceptable.

(Part II.)

1. A condition of hypersensitiveness to products of the haemolytic streptococcus has been described by various writers. It has been possible to demonstrate the development of this allergic state during the course of scarlet fever.
2. The preparation has been described of an extract representing the soluble intracellular products of the organism freed from diffusible substances.
3. Using this material the skin reactions in 74 cases of scarlet fever have been studied. In the first week of the illness all the reactions were negative or feebly developed, but in the fourth week 66 patients (almost 90%) gave positive reactions.
4. 28 of these cases were tested at weekly intervals; in these cases the positive reaction was sometimes present in the second, and usually present in the third week.
5. Age is an important factor in the development of this skin sensitivity. All the cases over 7 years of age developed the allergic reaction. The older age groups tended to become positive at an earlier stage than the younger children and their sensitivity became greater as judged by the intensity /

intensity of the skin reactions.

6. Normal persons are frequently sensitive to this type of preparation, but young children are rarely so. The reactions noted after scarlet fever cannot be regarded, therefore, as a recrudescence of a pre-existing skin sensitiveness.
7. Repeated skin testing in control cases produces no such increase in reaction.
8. Although in many cases skin sensitivity to H.S.E. and Dick toxin is inversely related, this relationship is not a constant one.
9. The possible significance of this allergic state in the causation of scarlatinal nephritis and scarlatinal arthritis needs further study.
10. A case of scarlatinal arthritis with a particul: :arly intense skin reaction has been described. This would appear to sharply differentiate scarlatinal arthritis from acute rheumatism.
11. The persistence of this allergic condition may be of importance in the development of the "rheumatic state". This possibility has been discussed. 3 cases tested a year later have retained their sensitivity to H.S.E. 1 of these /

these cases has developed chorea.

12. 160 persons not suffering from scarlet fever have also been skin tested with H.S.E. Age has an important influence on the results. The reaction appears to be inhibited in chronic cardiac disease and wasting conditions, but to a less extent in acute infections unless these be of exceptional severity.

13. The results in erysipelas contrast sharply with those in scarlet fever. In erysipelas the skin reaction is positive on admission to hospital and appears to remain so at all stages of the disease. In the absence of extreme illness a negative reaction in an adult patient should question the diagnosis of erysipelas. In young patients the skin reaction in this disease is still unknown.

14. A proportion of cases of puerperal infection show an increasing sensitivity as in scarlet fever. The possibility of this being a recrudescence of a pre-existing skin sensitiveness is difficult to exclude unless the reaction to H.S.E. be tested before infection. The relationship between the skin changes and the infecting organism needs further study.

15. At /

15. At the present stage the work is in so many respects incomplete that conclusions must be necessarily limited. It will only be possible to assess the importance of the results already obtained by following up each new line of investigation as it suggests itself, while trying not to lose our perspective of the problem as a whole.

16. It is doubtful if we can hope to make much real progress until the mechanism of these skin reactions is better understood, and their significance in relation to the vital processes in general better appreciated.

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